Commentary

Off-Label on the Table

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The headline in the Washington Post reads, *"FDA proposes to let drug companies undermine official safety warnings,"* but that is misleading at best and a downright error at worst.

Alas, this isn't a case of a bad headline written by an editor. Here's how the article begins:

"The Food and Drug Administration is proposing to allow pharmaceutical companies to undermine official safety warnings in sales presentations to customers."

For starters, 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 What the draft guidance addresses is the ability of pharmaceutical companies to present research published in peer-reviewed journals that goes beyond the information provided in the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 does not undermine anything. In fact, the reverse is true, it adds to scientifically acceptable, often cutting-edge information. And knowledge is power in pursuit of the public health.

Specifically, under the proposal, 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.

Knowledge is power in pursuit of the public health. Further, this language makes it clear that the FDA retains the right to object when such information *does not* meet this standard. It is by no means a Katy-bar-the door exercise. And since there is no definite "standard," FDA actions will be carefully watched. CDER'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.

Sid Wolfe of Public Citizen offers 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 – and it's more than a finesse. It's one of those 800-pound gorilla issues we've been pussyfooting around for too long. And now, at long last with the FDA appropriately leading the charge, it's time for a serious conversation.

The first thing to point out is that this agency action preempts attempts to legislate similar outcomes. According to the House Energy & 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. 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.

As PhRMA has said in the past, some of the regulations and guidances of the Food and Drug Administration (FDA) 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 their patients' individual healthcare needs and preferences.

Biopharmaceutical companies have the most complete and up-to-date information about the medicines that they research, develop and manufacture for use by patients. However, companies are often unable to proactively share valuable information about their medicines, especially for information that is not contained in the FDA-approved prescribing information (the package insert you often receive with a prescription), with physicians and other healthcare providers.

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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.
- **Sub-population data –** Information on the safety and effectiveness of medicines in sub-populations including gender and race. Such information can help healthcare 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 two or more therapies.
- **Pharmacoeconomic 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** – Information on new uses of approved medicines that are listed in major compendia and/or routinely reimbursed by the federal government and major payers. As the National Cancer Institute states, "Often, usual care for a specific type or stage of cancer includes the off-label use of one or more drugs."[1] Healthcare professionals help patients by applying new uses of approved drugs in "every specialty of medicine."[2] When patients are being prescribed medicines off-label, they deserve to know that their healthcare professionals have the latest information on these uses.

There is 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."

Facts do not cease to exist because they are ignored. And this is an issue with a lot of history – with only a small piece making it into the reporting of this week's FDA announcement. Let's look at the record.

According to a 2011 notice in the Federal Register:

> *The Food and Drug Administration (FDA) is announcing the establishment of a docket to assist with our evaluation of our policies on communications and activities related to off-label uses of marketed products, as well as communications and activities related to use of products that are not yet legally marketed for any use, we would like to obtain comments and information related to scientific exchange. FDA is interested in obtaining comments and information regarding scientific exchange about both unapproved new uses of products already legally marketed ("off-label" use) and use of products not yet legally marketed for any use.*

And the issue of "scientific exchange" comes front and center. According to the FR notice, *To assist with our evaluation of our policies on communications and activities related to off-label uses of marketed products, as well as communications and activities related to use of products that are not yet legally marketed for any use, we would like to obtain comments and information related to scientific exchange.*

The FR notice puts this request into perspective:

> *On July 5, 2011, a citizen petition was submitted by Ropes & Gray and Sidley Austin LLP on behalf of seven product manufacturers (Petitioners): Allergan, Inc.; Eli Lilly and Co.; Johnson & Johnson; Novartis Pharmaceuticals Corp.; Novo Nordisk, Inc.; Pfizer, Inc.; and sanofi-aventis U.S. LLC under 21 CFR 10.30. The citizen petition requested that FDA clarify its policies for drug products and devices governing certain communications and activities related to off-label uses of marketed products and use of products that are not yet legally marketed for any use. Specifically, the petition requests clarification in the following areas:*
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> 1. *Manufacturer responses to unsolicited requests;*
> 2. *Scientific exchange;*
> 3. *Interactions with formulary committees, payers, and similar entities; and*
> 4. *Dissemination of third-party clinical practice guidelines.*

For some time, FDA has been considering these issues and is currently evaluating our policies on sponsor or investigator communications and activities related to off-label uses of marketed products and use of products that are not yet legally marketed for any use. We have been considering what actions to take in the areas specified by the petitioners with respect to manufacturer responses to unsolicited requests; interactions with formulary committees, payors, and similar entities; and the dissemination of third-party clinical practice guidelines.

Specifically, the FDA asks:

- *How should FDA define scientific exchange?*
- *What types of activities fall under scientific exchange?*
- *What types of activities do not fall under scientific exchange?*
- *Are there particular types and quality of data that may indicate that an activity is, or is not, scientific exchange?*
- *In what types of forums does scientific exchange typically occur? Should the use of certain forums be given particular significance in determining whether an activity is scientific exchange or an activity that promotes the drug or device? If so, which forums?*
- *What are the distinctions between scientific exchange and promotion? What are the boundaries between scientific exchange and promotion?*
- *Generally, who are the speakers involved in scientific exchange, and who is the audience for their communications?*
- *Should the identity of the participants (either speakers or audience) be given particular significance in determining whether an activity is scientific exchange or an activity that promotes the drug or device? If so, which participants would be indicative of scientific exchange and which would be indicative of promotion?*
- *How do companies generally separate scientific roles and promotional roles within their corporate structures?*
- *How should the Agency treat scientific exchange concerning off-label uses of already approved drugs and new uses of legally marketed devices? Please address whether there should be any distinctions between communications regarding uses under FDA-regulated investigation (to support potential approval) and communications regarding uses that are not under express FDA-regulated investigation.*
- *How should the Agency treat scientific exchange concerning use of products that are not yet legally marketed (that is, products that cannot be legally distributed for any use outside of an FDA- or institutional review board (IRB)-approved clinical trial)?*
- *Should investigational new drugs and investigational devices be treated the same with respect to scientific exchange? Why or why not?*
- *Under 21 CFR 812.7(b), an investigational device is considered to be "commercialized" if the price charged for it is more than is necessary to recover the costs of manufacture, research, development, and handling. Similarly, FDA considers charging a price for an investigational drug that exceeds that permitted under its regulations (generally limited to cost recovery) to constitute "commercialization" of the drug (see 74 FR 40872 at 40890, August 13, 2009; 52 FR 19466 at 19467). What other actions indicate the commercialization of drug and/or device products? If there are differences in the steps taken to commercialize drug products and the steps taken to commercialize device products, either before or after approval, please explain these differences.*

And it's not just PhRMA – patient groups have weighed in as well. Some examples:

NORD:

At the same time, the government severely restricts what drug companies can say about new research and about off-label uses, thus cutting off information from the most knowledgeable sources. The Congress should seek new policies that permit drug companies to share appropriate information without fear of enforcement action.

OVARIAN CANCER NATIONAL ALLIANCE

In ovarian cancer, as in many oncology settings, patients receive "off-label" therapies, which are legal and often part of practice guidelines. Access to these therapies is critical to providing patients with the best possible care...

The Alliance is deeply concerned that these revisions will chill off-label use of drugs and the dissemination of scientific information about non-approved uses. We strongly urge FDA to reconsider these changes and remove any language that may curb patient access to medically-accepted and life-saving medications.

AND FROM BIO:

Current law deals with the important question of providing payers and others with meaningful information regarding the pharmacoeconomic benefits of medicines. However, implementation of Section 114 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) has undermined innovators' ability to meet requests for such information. The committee could evaluate how this important provision could be implemented in a less restrictive way to allow manufacturers to discuss more fully the value to the healthcare system of their innovations.

More broadly, provision of other truthful and non-misleading information to providers, payers, and patients also should not be impeded by unnecessary and cumbersome regulatory restrictions or requirements. Such approaches hinder users of medicines from accessing information that can help them use the medicines most effectively.

Much food for thought here, but two things in particular to mention:

* This is not an "out-of-the-blue" action by the FDA.
* It's not just about communications with physicians – but also with payer formulary committees.

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 health care economic information to MCO formulary committees: "competent and reliable scientific evidence."

But as Bob Temple commented, FDAMA 114 is "an interesting section, and its not entirely simple to figure out what's included and what's not included.

No kidding.

Even though there is no FDA guidance to explain the agency's understanding of "competent and reliable scientific evidence," PhRMA developed a draft guidance, which was submitted to the FDA in June 1998. In its draft, PhRMA sought input from the International Society for Pharmacoeconomics and Outcomes Research, the Society for Medical Decision Making, the Academy of Managed Care Pharmacy, the American Pharmaceutical Association, and other groups.

In its submission to the FDA, PhRMA explained the history behind Section 114 and proposed guidance on the following terms used in the new law:

- Health care economic information.
- Managed care or other similar organizations.
- Formulary committee or other similar entity.
- Directly related to an approved indication.
- Competent and reliable scientific evidence.

The PhRMA proposal took an approach to interpretation consistent with Congress's intent that Section 114 would increase the dissemination of outcomes research information by product manufacturers to MCOs. PhRMA concluded that the term "health care economic information" should include all forms of economic analysis so the guidance could adapt to new and evolving outcomes research methods.

One of the phrases in Section 114 that is difficult to interpret 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.

The standard set by Section 114, "competent and reliable scientific evidence," is the same standard used by the Federal Trade Commission (FTC) when assessing the adequacy of substantiation for manufacturer claims involving OTC drugs and products affecting environmental health. That standard requires transparency of methods and use of methods accepted by experts in the field. In its proposal, PhRMA recommended that the FDA follow long-established FTC interpretation of the competent and reliable scientific evidence standard.

The full FR Notice on "Communications and Activities Related to Off-Label Uses of Marketed Products

and Use of Products Not Yet Legally Marketed; Request for Information and Comments" can be found at http://www.gpo.gov/fdsys/pkg/FR-2011-12-28/pdf/2011-33188.pdf.

In October 2012, PhRMA issued a white paper, asking the FDA for guidance on the supporting evidence drug companies need for the health care economic data they send to formulary managers should specifically allow for use of a range of data sources, not limited to adequate and well-controlled clinical trials.

The white paper urges the agency to develop formal regulatory guidance on Sec. 114 of the FDA Modernization Act of 1997, which allows drug companies to proactively disseminate health care economic information to formulary committees within certain limitations.

The white paper outlines a number of data elements that should satisfy the competent and reliable scientific evidence standard. They include: methods for establishing economic costs and consequences that are widely accepted by experts in the field using a clear, pre-defined study protocol; an "accurate and balanced assessment of the economic consequences of a drug therapy, consistent with the current weight of credible evidence"; a representative study population; and information that allows the reader to determine how the research was conducted.

PhRMA recommends 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."

For example, "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."

PhRMA argues that FDA should not consider such a statement a comparative clinical claim, which would trigger the "substantial evidence" requirement involving clinical trials.

Companies should be permitted to disseminate data on the "real world" economic implications of a therapy on health outcomes, according to the white paper. For example, "if a manufacturer conducts a competent and reliable study investigating the impact of a drug indicated for the treatment of diabetes mellitus on costs associated with cardiovascular care, the manufacturer should be permitted to proactively disseminate such data to appropriate audiences."

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, do the opportunities outweigh the risks? There are a few ways to approach this.

There's the First Amendment question. Did the *Caronia Philharmonia* impact the way FDA views off-label promotion within the context of the free-and-fair dissemination of scientific data? It was certainly a part of the cogitation process.

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 the least of which is reimbursement. But such negative unintended consequences are important to discuss and consider. Any company that chose 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 route.

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.

REFERENCES

1. See National Cancer Institute, Off-Label Drug Use in Cancer Treatment, available at http://www.cancer.gov/cancertopics/druginfo/offlabeldrug.
2. Christopher M. Wittich, et; al., Ten Common Questions (and Their Answers) About Off-label Drug Use, Mayo Clinic Proceedings, available at http://www.mayoclinicproceedings.org/article/S0025-6196(12)00683-0/fulltext#sec3.