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FDA's Off-Label Comms Guidance Is A Reluctant Step Forward

By **Jeffrey Shapiro and Lisa Dwyer** (November 6, 2023, 2:37 PM EST)


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Last month, the U.S. Food and Drug Administration published a draft guidance making recommendations for permissible proactive communications to health care providers regarding unapproved uses of approved or cleared medical products, i.e., off-label uses.

Remarkably, this draft is an update of a prior draft guidance issued almost 10 years ago. At this rate, one wonders whether a final guidance will see the light of day before 2033.

In any event, we do not propose to provide a detailed description of the guidance, which has been ably described in other publications. Suffice it to say that its biggest innovation is the creation of a new effective safe harbor for certain proactive firm-generated presentations of off-label information to health care providers.

The guidance also allows firms to distribute materials from independent clinical practice resources, i.e., digital resources "that contain medical and scientific information in a wide range of topics developed by subject matter experts in various medical specialty fields" in addition to reprints, reference texts and clinical practice guidelines, which were sanctioned by the previous version of the guidance.

Additionally, the guidance allows for source material and covered communications to be shared in broader channels, i.e., it expands the settings to include the internet, email and medical conference booths, so long as certain guardrails are met.

In other words, the FDA has deepened and widened its safe harbor for the dissemination of truthful and nonmisleading scientific information about off-label uses of medical products.

We thought it might be helpful to step back and look how this draft guidance fits within the FDA's general opposition to the dissemination of off-label information by drug and device manufacturers.

It is well-known that, once the FDA approves a device or drug for marketing for any use, physicians lawfully may use it for other uses. Because many drugs and devices have more than one possible use, off-label use is not uncommon. Indeed, all agree that off-label uses offer important benefits to patients and sometimes even become the standard of care.

The FDA views off-label use as undermining its role as gatekeeper against unsafe or ineffective devices and drugs. The FDA has significant leverage in dictating whether the product may be marketed and how

it will be labeled — for its first use. The moment, however, a device or drug lawfully enters commerce for any one use, the FDA loses this leverage for other uses.

Among other things, it becomes the FDA's burden to prove that claims about the safety or efficacy of the off-label use are false or misleading. The burden would shift back to the manufacturer if it were to request a modification of the FDA-approved labeling to add the new use. But if sales are sufficiently robust, a sponsor may not have a financial incentive to do so.

In such cases, the new use permanently escapes the kind of control that the FDA has over the initial approval. The FDA has sought to partially reassert control by preventing sponsors from promoting off-label uses of their products, which potentially incentivizes them to try to bring the new use on-label.

Because the Federal Food, Drug and Cosmetic Act does not expressly prohibit off-label promotion, the FDA developed a legal theory several decades ago that such promotion creates a new intended use requiring separate approval under the FFDCA. Until such approval is granted, according to the FDA, the off-label promotion adulterates or misbrands the product.

This legal theory has not fared well in federal court. In the past 25 years or so, the FDA has consistently lost ground in disputes over its ability to prohibit off-label promotion.

The problem the federal courts see with the FDA's approach is that physicians may lawfully use drugs and devices off-label. Therefore, the FDA is suppressing the free flow of truthful and nonmisleading speech to highly trained experts engaged in the lawful practice of medicine.

Typically, under the First Amendment, the government is not allowed to do so. And worse, the FDA does so by targeting a class of disfavored speakers, i.e., manufacturers, while other speakers may provide exactly the same information without legal sanction.

Under the First Amendment, such content and speaker-based restrictions can be accepted only if, among other things, they are narrowly drawn to directly advance the FDA's interest in obtaining premarket review of all uses.

The FDA has seldom been able to persuade the federal courts that this test has been met, and the agency's losses in court have led to the current guidance and its precursors. Two historical examples follow.

Example 1

In Washington Legal Foundation v. Friedman in the U.S. District Court for the District of Columbia in 1998, the plaintiff challenged restrictions on the dissemination of reprints, scientific texts and communications related to continuing medical education.

The district court enjoined enforcement of the restrictions, agreeing with the plaintiff that they violated the First Amendment. The FDA responded by announcing a change to its enforcement policy.

The agency declared that it would (1) generally treat off-label communications as evidence of intended use, and (2) establish safe harbors for the dissemination of reprints, scientific texts and certain communications related to continuing medical education. As a result of the FDA's about-face, the U.S. Court of Appeals for the District of Columbia Circuit vacated the district court's injunction as moot.

Following the WLF litigation, the FDA published a Federal Register notice stating that so long as manufacturers met certain requirements, they could distribute certain journal articles and reference texts to discuss off-label uses.

That Federal Register notice was superseded by two guidances that were precursors of the new guidance, and now the new guidance as well. Importantly, the 2014 version of the guidance stated that manufacturers should not summarize journal articles, reference texts, or clinical practice guidelines for health care providers. That is what the new draft guidance now permits.

Example 2

Amarin Pharma Inc. filed a declaratory judgment action challenging the FDA's off-label speech policy as applied to truthful statements that Amarin wanted to make to health care providers about an off-label use of its drug, Vascepa.

In that case, the off-label statements at issue were supported by a Phase 3 adequate and well-controlled clinical trial. In 2016, the U.S. District Court for the Southern District of New York granted Amarin a preliminary injunction, and found that the First Amendment prohibits the FDA from bringing an enforcement action "based on truthful promotional speech alone." The case was **settled** without a final decision.

During that litigation, Janet Woodcock, then the director of FDA's Center for Drug Evaluation and Research, issued a letter. The Woodcock letter stated that the FDA would not object to the company's dissemination to health care providers of summaries of the results of the Phase 3 trial at issue, if the summaries are truthful, nonmisleading and unbiased.

Since the Woodcock letter, companies have asked about when they can share their own firm-generated truthful, nonmisleading and unbiased summaries of off-label information related to clinical trial results. That is the primary question that the FDA answered with the new guidance.

Although the new guidance opens the door a bit wider on manufacturer speech about off-label uses, it does so begrudgingly. In the guidance, the FDA takes a severe tone, implying that these lines are very firm and not to be crossed. It is like a parent who never allows a child to eat chocolate candy, but makes an exception, "this one time" and "only if you behave."

Thus, the new guidance makes many statements about the importance of being truthful and nonmisleading, when that requirement has never been in dispute.

The guidance does give helpful examples of data sources and modes of presentation that the FDA would agree are truthful and nonmisleading. Nonetheless, the FDA's tone might give the industry the misimpression that these examples represent the outer limit.

In fact, these recommendations should be regarded as a floor and not a ceiling. There are many other sources of data and modes of presentation not outlined in the guidance that could be considered truthful and nonmisleading.

The guidance has a fascinating admonition against "persuasive marketing techniques" defined as marketing techniques that do not rely on science, like celebrity endorsements and gifts.

This might be taken as evidence of a low regard for the ability of the medical profession to resist celebrities and trinkets when making decisions about patient care. Indeed, the FDA cites an apparently burgeoning body of literature to back this up.

Still, the FDA's admonition brings to mind a long-ago counter admonition from U.S. District Judge Royce Lamberth in the Washington Legal Foundation case:

> In asserting that any and all scientific claims about the safety, effectiveness, contraindications, side effects, and the like … are presumptively untruthful or misleading until the FDA has had the opportunity to evaluate them, FDA exaggerates its overall place in the universe.

The bottom line is the guidance is more of the same. It does not decisively resolve the First Amendment disconnect between the FDA and the federal courts. What it does do is provide a manufacturer with a somewhat larger safe harbor than was previously the case.

Our experience tells us that situations will arise where the FDA's latest guidance will not provide a clear answer. In those cases, the crucial consideration is that all statements must be truthful and not misleading. If they are, it will pose the maximum challenge for the FDA, because, if the agency wishes to prohibit such statements, it faces a high bar in court.

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