Portfolio Media. Inc. | 230 Park Avenue, 7th Floor | New York, NY 10011 | www.law360.com
Phone: +1 646 783 7100 | Fax: +1 646 783 7161 | customerservice@law360.com

What Pharma Cos. Must Know About FDA Off-Label Guidance

By **Jacqueline Berman and Maarika Kimbrell** (October 27, 2023, 5:26 PM EDT)


Jacqueline Berman


Maarika Kimbrell

The U.S. Food and Drug Administration issued a much-awaited draft guidance on Oct. 24 revising its approach to the dissemination of scientific information on unapproved uses of approved or cleared medical products.

This draft guidance follows a series of challenges to the FDA's prior promotional restrictions on off-label communications and citizen petitions from company coalitions.

On the whole, while the draft guidance does not represent an about-face on the FDA's approach to communications regarding unapproved uses for approved products, it does expand the scope of such communications that the FDA is willing to permit, and clarifies issues that the industry has grappled with for many years regarding circumstances under which scientific information regarding such uses can be provided to the health care community.

Specifically, the draft guidance outlines communications that, if undertaken in accordance with the guidance, would help firms avoid enforcement action by the agency, including, most notably, certain content created by a firm about its own product.

Summary of the Draft Guidance

The draft guidance addresses circumstances under which firms can disseminate published scientific or medical journal articles, including reprints, and firm-generated presentations regarding the same.

It also addresses published clinical reference resources — clinical practice guidelines, reference texts and independent clinical practice resources — that concern scientific information on unapproved uses, or SIUU, of approved or cleared medical products.

In doing so, the FDA states that it "has sought to strike a careful balance between supporting [health care provider] interest in scientific information about unapproved uses of approved/cleared medical products to inform clinical practice decisions for the care of an individual patient, and mitigating the potential that the government interests" in the statutory premarket approval requirements would be undermined.

In light of these efforts at goal balancing, the FDA has proposed an approach in developing and

disseminating SIUU communications that would avoid enforcement by the FDA by not being considered evidence of a new intended use of a product. To fall within this enforcement policy, companies disseminating SIUU information must meet certain criteria.

First, any communications regarding SIUU would need to be based on medical journal articles or published clinical reference resources that meet certain FDA-enumerated publication standards, and the communications would need to be truthful, nonmisleading, factual and unbiased.

To meet this standard, the SIUU communications would need to provide health care providers all information that may be necessary to understand the "strengths and weaknesses and validity and utility" of the information being conveyed, according to the guidance.

This would require firms to include certain disclosures as part of SIUU communications, many of which are similar to the FDA's prior Guidance for Industry Distributing Scientific and Medical Publications on Unapproved New Uses, referred to as the reprint guidance, as well as the FDA's guidance on medical product communications consistent with FDA-required labeling.

Second, the source publication that serves as the basis for the SIUU communication would need to be scientifically sound and would need to provide information that is relevant to health care providers making clinical practice decisions regarding the care of an individual patient — i.e., the information would need to be clinically relevant.

To meet this standard, the source publication would need to, at a minimum, meet generally accepted design and methodological standards for the particular type of study or analysis, taking into account established scientific principles and current scientific knowledge.

This would include randomized, double-blind, concurrently controlled superiority studies, as well as other "well-designed and well-conducted trials," the guidance says. Real-world data and evidence may also meet this standard, depending on the characteristics of the data and the nature of the specific analyses.

Conversely, studies without adequate comparison or control groups, individual case reports and reports that do not contain sufficient detail to permit a scientific evaluation of the underlying information would not meet this standard.

Early-stage studies are also "unlikely to be sufficiently reliable by themselves to allow for a determination of clinical relevance," according to the guidance. Whether any particular study or source publication meets this standard would be an individualized analysis based on any scientific or data limitations.

Unlike the reprint guidance, which prohibited firms from summarizing or characterizing a source publication, the SIUU guidance permits firms to present SIUU information that is based upon a qualifying source publication provided that certain factors are met.

Specifically, the presentation would need to clearly and prominently include required disclosures and would not be permitted to use "persuasive marketing techniques," including, but not limited to, celebrity endorsements, premium offers and gifts.

The FDA would look for any indication that the firm is attempting to influence health care providers to

reach a positive conclusion about the unapproved use, other than via the unbiased scientific content of the communication.

SIUU information presentations would also need to be separate and distinct from promotional communications, a concept that may not be new to many in the industry.

This would mean separating promotional content and SIUU information into different communications, as well as using vehicles, channels and venues for sharing SIUU communications that are different and distinct from those used for promotional communications, such as the current practice of maintaining a clear division between a firm's marketing/promotional content and personnel and medical affairs activities.

For smaller firms where such a division may not be possible, the FDA states that the company "should ensure that SIUU communications are clearly identified and distinct from promotional communications about approved uses."

To accomplish these ends, the FDA also recommends that websites contain separate pages for promotional communications and SIUU communications and that these pages not cross-link to each other.

When communicating SIUU information, firms should only use platforms that allow for full compliance with the guidance, including the inclusion of all necessary disclosures. This means that certain social media platforms with space limitations may not be appropriate.

The FDA does state, however, that a firm could use a social media platform to announce a new publication and link to a website with an SIUU communication that is compliant with the guidance.

Moreover, to ensure that health care providers fully understand an SIUU communication, the FDA recommends that firms use plain and clear language for any company-developed portions of a communication, including the FDA-recommended disclosure.

The FDA also states that firm-generated presentations should be accompanied by the full underlying reprint. However, per the FDA:

[F]irms should not rely upon the accompanying reprint(s) to provide information that is material to the representations made in the firm-generated presentation; all information material to the representations… should be included with those representations within the firm-generated presentation.

Finally, according to the draft guidance, firm presentations should not:

- Imply that the information "represents larger or more general experience with the medical product than it actually does";
- Decontextualize the presented information such that health care providers do not have the information necessary to interpret the strengths, weaknesses, validity and utility of the data;
- Represent or suggest product safety or efficacy in a way that is "not consistent with the reprint";

- Make conclusions or representations regarding an unapproved use, "even if an accurate reflection of the statements in the reprint, without attributing that statement expressly to the reprint" and without contiguous disclosures regarding author-firm affiliations;

- Employ statistics to imply the clinical significance or validity of data when not supported; or

- Otherwise use tables, graphs or presentational elements to distort or misrepresent the data.

Key Takeaways and Conclusions

On the whole, the new draft SIUU guidance would provide some necessary clarity with respect to the communication of scientific information regarding unapproved uses of approved products, providing companies with greater certainty on the scope of scientific information that may be disseminated, as well as how such information may be communicated to the medical community.

Notably, however, and as specifically pointed out by the FDA, dissemination of SIUU information in accordance with the new guidance would not be the only way that companies may engage in communications regarding unapproved uses of approved products.

Companies may still avail themselves of the FDA's guidance on responding to unsolicited requests for off-label information about prescription drugs and medical devices, industry-supported scientific and educational activities, and drug and device manufacturer communications with payors, formulary committees, and similar entities — and associated statutory provisions.

The FDA further states:
[I]t has long been FDA policy not to consider a firm's presentation of truthful and non-misleading scientific information about unapproved uses at the planned sessions and presentations at medical or scientific conferences to be evidence of intended use when the presentation is made in non-promotional settings and not accompanied by promotional communications.

Accordingly, the SIUU guidance would provide companies with an additional avenue to communicate scientific information to the medical community.

In some ways, the draft SIUU guidance would expand the scope of information on which firms would be able to rely when disseminating information regarding unapproved uses of approved products.

Unlike the FDA's prior guidance on the dissemination of reprints that required that studies be well-controlled clinical investigations, the SIUU guidance provides for other kinds of studies so long as they are scientifically sound and clinically relevant.

This, however, would require firms to assess whether the new FDA standard is met for source publications and firm-generated material. It also would require firms to periodically reassess source publications to confirm that they continue to meet FDA standards — e.g., to confirm that there have not been any new findings that may undermine a publication's clinical relevance.

This would require that companies establish processes to scientifically and clinically assess source publications, both initially and following initial approval of a publication's use.

In other ways, however, the SIUU guidance may be intended to restrict the scientific information that

may be disseminated by companies.

Under the FDA's regulations and the agency's long-standing policy, the agency does "not intend to restrict the full exchange of scientific information concerning [a] drug, including dissemination of scientific findings in scientific or lay media." This did not rule out the presentation of internally generated data that may not yet be published.

Under the SIUU guidance, however, companies with approved products that intend to disseminate SIUU information may only rely on published scientific or medical journal articles and clinical reference resources to fit within the FDA's communicated enforcement policy. This would not, notably, include unpublished data on file.

Finally, while not explicitly stated, the SIUU guidance would clarify the question regarding whether information on unapproved uses that are disseminated in the form of reprints and clinical practice resources, and other presentations based on the same, may be proactively distributed by a company or whether they may only be distributed in response to an unsolicited request for information, an area that has historically raised questions within the industry.

Based on the guidance's discussions regarding posting SIUU information to company websites and dissemination via social media, the FDA appears to settle this question by indirectly stating that SIUU information that complies with the guidance may be proactively communicated.

Affected stakeholders may wish to submit comments to the FDA regarding the policies proposed in the draft guidance — comments are due by Dec. 26 — and begin to consider how the FDA's draft guidance recommendations may be successfully implemented.

Jacqueline Berman and Maarika Kimbrell are partners at Morgan Lewis & Bockius LLP.