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Beyond Reprints for Scientific Information on Unapproved Uses

Revised Draft FDA Guidance Expands Scope of Permissible Proactive Off-Label Communications

This week, FDA published new revised draft guidance, ***Communications From Firms to Health Care Providers Regarding Scientific Information on Unapproved Uses of Approved/Cleared Medical Products: Questions and Answers*** (hereinafter *SIUU Communications Guidance*), to reframe recommendations for permissible proactive communications to healthcare providers (HCPs) regarding unapproved uses of approved or cleared medical products.[1] In addition to reaffirming established scientific exchange pathways for sharing off-label information,[2] the new guidance redefines approaches for proactively sharing certain "scientific information on unapproved uses" (SIUU) to HCPs – including reprints, clinical practice guidelines (CPGs), and, most importantly, a new category for firm-generated presentations of scientific information on unapproved uses.

This new category represents a significant change in FDA's current policy. The new guidance supersedes the agency's 2014 revised draft guidance, *Distributing Scientific and Medical Publications on Unapproved New Uses – Recommended Practices* (hereinafter *2014 Draft Reprints Guidance*), reflecting FDA's ongoing efforts to adjust policies and recommendations related to product communications consistent with the First Amendment.

As described in the new draft guidance, SIUU communications should be:

— Based on an appropriate "source publication" describing a "scientifically sound and clinically relevant" study or analysis;

— Truthful, non-misleading, factual, and unbiased;

— Accompanied by all information necessary for HCPs to interpret the strengths, weaknesses, validity and utility of the information; and

— Presented without persuasive marketing techniques and appear separate and distinct from promotional communications, among other considerations.

Consistent with other FDA guidance and policies that create safe harbors for non-promotional communications, FDA does not intend to treat compliant SIUU communications, standing alone, as evidence of a new intended use.

SIUU COMMUNICATIONS GUIDANCE SCOPE

As described in the draft guidance, a firm's[3] SIUU Communication must meet the following criteria:

- ***Pertain to an unapproved use of an approved or cleared medical product*** (i.e., human prescription and non-prescription drugs and biologics, medical devices, and animal drugs).
  - The guidance does *not* apply to purely investigational medical products (i.e., drugs or devices not yet approved or cleared for any use).
- ***Intended for HCPs making clinical practice decisions for the care of individual patients***.
  - The guidance does *not* apply to communications to consumers, patient groups, payers, or researchers.[4]
- ***Based on an appropriate "source publication."***
- ***Distributed as one of the following types of communications:***
  - Reprint;
  - Clinical reference resource (i.e., clinical practice guideline (CPG), reference text, or an independent clinical practice resource); or
  - Firm-generated presentation of scientific information *from an accompanying published reprint*.

While the guidance significantly expands the scope of permissible off-label communication, the guidance also limits the expanded safe harbor for firm-generated off-label presentations to presentations pertaining to and *accompanied by* a published reprint. From a practical perspective, the guidance blesses off-label "reprint carriers" as well as other firm-generated presentations, including digital, video or other media, if the reprint accompanies the presentation (e.g., presumably, via link or attachment). Thus, the SIUU Communications Guidance suggests that the expanded communication pathway will not apply to firm-generated communications pertaining to other (non-reprint) source publications.

CRITERIA FOR SOURCE PUBLICATIONS – SCIENTIFICALLY SOUND AND CLINICALLY RELEVANT

Source publications used as the basis for a SIUU communication must be *scientifically sound* and *clinically relevant.* Although "***scientifically sound***" is a term used in the 2014 Draft Reprints Guidance, FDA clarifies and expands the scope to include examples beyond adequate and well-controlled studies and meta-analyses, including:

- *Other well-designed and well-conducted trials* if they meet generally accepted design and other methodological standards for the particular type of study or analysis.
- *Real-world data and associated real-world evidence,* which may, depending on the nature of the analysis and characteristics of the data, be considered both scientifically sound and clinically relevant. The draft guidance notes that such data should be derived from analyses that are prespecified, with protocols and statistical analyses plans finalized prior to conducting the prespecified analyses, and with data integrity carefully monitored and maintained.

"***Clinically relevant***" is a new element of the evidentiary standard, which the draft guidance explains as meaning that the study or analyses should provide information pertinent to HCPs making clinical practice decisions for individual patients.

According to FDA, studies and communications that are unlikely to be scientifically sound and clinically relevant include:

- Early-stage scientific data, including pre-clinical and Phase I and II studies;
- Studies without an adequate comparison or control group, isolated case reports and other reports that lack enough detail to permit scientific evaluation;
- Communications or publications that distort studies (e.g., by inaccurately describing or interpreting results) or that include fraudulent data or that contain flaws that make the study or analysis unreliable; and
- Studies or analyses that are no longer clinically relevant (e.g., because subsequent research has established the findings as unreliable).

INFORMATION TO INCLUDE IN SIUU COMMUNICATIONS

The draft guidance details the information that should accompany an SIUU communication to help ensure it is truthful, non-misleading, factual and unbiased and contains sufficient information for HCPs to interpret the strengths, weaknesses, validity and utility of the SIUU. Much of this information is similar to what FDA recommended under the 2014 Draft Reprints Guidance. With limited exceptions, FDA recommends that firms include all of the following information as part of SIUU communications:

- A statement that the unapproved use(s) of the medical product has not been approved by FDA and that the safety and effectiveness of the medical product for the unapproved use(s) has not been established;
- A copy of the most current FDA-required labeling (or a mechanism for obtaining the labeling, as appropriate);
- Statements disclosing the FDA-approved indication (including any limitations) and certain safety information from the product's FDA-required labeling and any risk evaluation and mitigation strategy (REMS), if applicable;
- A financial conflict of interest disclosure statement for any authors, editors, or other contributors to publication(s) included in the SIUU communication;
- The publication date of any referenced or included publication(s); and
- If not included in the source publication, a description of all material aspects and limitations of study design, methodology, and results, and any conflicting conclusions from other relevant studies.

Additional criteria and considerations specific to each type of SIUU communication, including firm-generated presentations, are detailed in Q4 of the draft guidance. Recommendations pertaining to reprints and clinical reference resources are similar to those in the 2014 Draft Reprints Guidance.

RECOMMENDATIONS FOR PRESENTING SIUU

The SIUU Communications Guidance includes several recommendations for presenting SIUU, briefly summarized below:

1. **Clearly and prominently present all disclosures.**

   All recommended disclosures (see above) should appear clearly and prominently. Since FDA does not dictate the form of communication, the format and medium can vary (and may include, for example, print, digital, or conference booth). For audio and video presentations, FDA recommends that disclosures appear in both audio and text at the same time. Firm-generated presentations should include an additional disclosure statement: "This presentation was developed by FIRM X."

2. **Do not use persuasive marketing techniques.**

FDA views "persuasive marketing techniques" as an "effort to convince the HCP to prescribe or use the product for the unapproved use," and therefore as evidence of a new intended use for the product. Although the draft guidance provides examples of "persuasive marketing techniques" – such as celebrity endorsements, premium offers, and gifts – the full scope of techniques remains uncertain. For example, meals and speaker programs are alluded to in the footnoted references. Further, FDA's perspective on language choice (e.g., use of claims and characterization of data) and other common features of promotion (e.g., glossy and colorful presentation styles) is notably absent from this description and leaves room for interpretation.

3. **Do not mix with promotional communications.**

SIUU should also be "separate and distinct" from promotional communications about the product. FDA provides the following specific recommendations applicable to various communication forms:

- *Online communications*: Do not link from promotion to SIUU.
- *Email communications*: Share SIUU and promotional information in separate emails.
- *Medical conference booths*: Divide the booth space and keep SIUU separate, distinct, and clearly identified as SIUU.

Although the above examples help clarify FDA's thinking, questions remain about practical application and limitations, including when FDA may view SIUU information "together with a promotional communication." FDA's use of the term *separate web page* instead of *website* is curious and could be interpreted as permitting SIUU and promotional content within one website but different webpages. Similarly, FDA recommends the use of dedicated vehicles, channels, and venues for SIUU when "available," but does not provide a definition or limits to the concept of "availability." Firms will likely grapple with these and other questions as they operationalize this guidance.

4. **Share through appropriate media.**

Firms should consider the features and functionality of different media and platforms for SIUU communications and adjust their approach accordingly. For example, a character-space limited platform would not accommodate all recommended disclosures and information consistent with the draft guidance. In such case, FDA recommends a statement that does not mention a product (e.g., "New Publication for Health Care Providers – phase 3 trial results for an investigational treatment for [disease X]"), followed by a link to the SIUU communication.

5. **Use plain language.**

To support HCP comprehension, FDA recommends plain language in any firm-generated portions of an SIUU communication, including recommended disclosures. Despite HCPs' specialized training, FDA believes that clear, concise, well-organized explanations that avoid complexities (e.g., technical jargon, passive voice, long sentences) facilitate HCP understanding.

KEY TAKEAWAYS

The SIUU Communications Guidance represents a significant step in FDA's First Amendment policy, particularly considering the permissible *public* nature of proactive SIUU communications. Traditionally, FDA's safe harbors for off-label information have largely been limited to defined audiences and limited forums (e.g., scientific/medical congress presentations, responses to unsolicited requests, payor communications). Thus, the new draft guidance represents an important departure from the agency's traditional approach, providing permission to share certain information more freely. Its nod to real world data and associated real-world evidence is also a notable broadening of the kinds of information that FDA might consider scientifically sound and clinically relevant in this context.

Nevertheless, despite the significance of the guidance in evolving FDA's First Amendment policy, considerable limitations and ambiguities remain to be addressed. First, the draft guidance still raises concerns under the First Amendment. For example, the draft guidance's restrictions to a "source publication" may not be sustainable. Consider whether proactive firm-generated presentations that are truthful, not misleading, factual, and unbiased are permissible under the First Amendment if based on reliable scientific or medical information, including Phase II studies. In addition, limiting firm-generated presentations of SIUU to an *accompanying published reprint* may restrict the ability of firms to share SIUU based on other data or information that might meet the "scientifically sound and clinically relevant" standard. Indeed, one industry trend has been to make available studies and analyses, including posters and abstracts, for prescription drug products through company-sponsored medical and scientific websites and social media channels. The recommendations articulated in the guidance limit some current approaches for SIUU and may be vulnerable under the First Amendment.

Second, without more clarity, we envision that companies will struggle applying the newly described evidentiary standard of "scientifically sound and clinically relevant." Presumably, this is a higher bar than FDA's "scientifically appropriate and statistically sound" standard articulated in the draft guidance, *Medical Product Communications That Are Consistent With the FDA-Required Labeling — Questions and Answers*, which still proves challenging to implement in promotional communications.

Third, companies will need to carefully consider practical limits and guardrails for maintaining separation between SIUU communications and promotional activities. This includes not only evaluating boundaries for external communications and activities, but also considering the role of internal and external stakeholders. For example, who should be responsible for SIUU communications and who may provide input on firm-generated presentations? What role, if any, should a sales force have in relation to SIUU? Would a prominent KOL sharing SIUU on a company's behalf be viewed as a persuasive marketing technique?

These are only some of the questions we have been considering as we think about the practical application of the SIUU Communications Guidance. We will continue to explore the guidance and welcome your questions.

Comments on the draft guidance are due to FDA by December 26, 2023.

[1] FDA Notice of Availability; 88 Fed. Reg. 73031 (Oct. 24, 2023), *available at* https://www.federalregister.gov/public-inspection/2023-23372/guidance-communications-from-firms-to-health-care-providers-regarding-scientific-information-on; FDA Draft Guidance, Communications From Firms to Health Care Providers Regarding Scientific Information on Unapproved Uses of Approved/Cleared Medical Products Questions and Answers (Oct. 2023), *available at* https://www.fda.gov/media/173172/download.

[2] FDA has previously issued guidance in the realm of scientific exchange for non-promotional communications related to unapproved uses of approved or cleared medical products, including:

- *Guidance for Industry: Industry-Supported Scientific and Educational Activities* (November 1997)
- *Draft Guidance for Industry: Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products—Recommended Practices* (June 2014)
- *Draft Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices* (December 2011)
- *Guidance for Industry and Review Staff: Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities — Questions and Answers* (June 2018)
- FDA Memorandum: *Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products* (January 2017)

[3] The term "firm" is broadly defined to include applicants, sponsors, requestors, manufacturers, packers, distributors, licensees of those entities, as well as any persons or entities communicating on their behalf.

[4] For guidance on pre-approval communications with payors, see FDA's 2018 Draft Guidance, *Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities – Questions and Answers*. The draft guidance explains that FDA is separately soliciting public comment on the topic of a firm's communications with researchers.