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Client Alert

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FDA Finalizes Guidance on Scientific Information on Unapproved Uses (SIUU)

Final Guidance Further Expands Scope of Permissible Proactive Off-Label Communications

On January 6, 2025, FDA finalized its guidance entitled *Communications From Firms to Health Care Providers Regarding Scientific Information on Unapproved Uses of Approved / Cleared Medical Products* (hereinafter Final SIUU Guidance)[i] which provides the Agency's recommendations for permissible proactive communications to healthcare providers (HCPs) regarding unapproved uses of approved or cleared medical products. The Final SIUU Guidance replaces draft guidance issued in 2023, with several updates including three key changes to the Agency's policy:

1. **FDA no longer limits firm-generated presentations of SIUU to information from an accompanying reprint.** Firms may now develop firm-generated presentations of SIUU summarizing the other permissible source publications, including clinical practice guidelines (CPGs) (among others).

2. **FDA simplifies the scientific standard for SIUU from "scientifically sound and clinically relevant" (SS + CR) to "scientifically sound" (SS).**

3. **FDA acknowledges that scientifically sound studies can include early phase and other studies that were unacceptable in the 2023 Draft Guidance.**

The Final SIUU Guidance is in many ways consistent with the 2023 Draft Guidance, but there are some notable differences that will require industry to update current approaches to SIUU analysis and implementation. These differences are the focus of this client alert.

FDA PERMITS FIRM GENERATED PRESENTATIONS FOR *ALL* SIUU SOURCE PUBLICATIONS

Consistent with the 2023 Draft Guidance, the Final SIUU Guidance permits firms to proactively distribute four forms of source publications discussing unapproved uses of approved / cleared medical products:

- Published scientific or medical journal articles (reprints)
- Published clinical reference resources:
    - Clinical practice guidelines (CPGs)
    - Scientific or medical reference texts
    - Materials from digital clinical practice resources

Notably, the Final SIUU Guidance allows firms to distribute a firm-generated presentation summarizing *any* of the above four types of source publications. The 2023 Draft Guidance had restricted the use of firm-generated presentations to reprints only. This is one of the most significant changes in the Final SIUU Guidance, particularly as it relates to the distribution of firm-generated presentations on CPGs.

FDA also provided two examples that help clarify the Agency's intent with respect to the fourth category of SIUU: "materials from digital clinical practice resources." Although FDA notes in the Final SIUU Guidance that it "does not endorse any particular digital clinical practice resource," it includes Medscape and UptoDate as two specific examples in the category.

FDA REMOVES "CLINICALLY RELEVANT" FROM THE SCIENTIFIC STANDARD FOR SOURCE PUBLICATIONS

The Final SIUU Guidance simplifies the scientific standard for SIUU from "scientifically sound and clinically relevant" (SS + CR) to "scientifically sound" (SS). "Scientifically sound" was a term long used as an element of the evidentiary standard for permissible off-label reprints.[ii] The 2023 Draft Guidance introduced "clinically relevant" as a new element, stating that the SIUU study or analysis should provide information pertinent to HCPs making clinical practice decisions for individual patients. In our experience, industry found the "clinically relevant" element of the SIUU analysis subjective and challenging to implement. Removal of "clinically relevant" from the scientific standard for SIUU communications is a welcome update.

FDA REVERSES COURSE AND ADMITS THAT EARLY STAGE AND CERTAIN OTHER STUDIES CAN BE "SCIENTIFICALLY SOUND"

Another common source of industry frustration with the 2023 Draft Guidance was the language limiting use of "early-stage" clinical data (including Phase II data) in SIUU communications because it would be unlikely to meet the clinically relevant standard.[iii] Similarly, the 2023 Draft Guidance recommended against the use of certain other studies, including those without an adequate comparison or control group, because they generally would not be scientifically sound or clinically relevant. With the removal of the clinically relevant standard, FDA has acquiesced to using certain early-stage data for SIUU communications that meet the scientifically sound standard. As an example, FDA states that "a scientifically sound study could include an early-phase randomized, double-blind, parallel assignment clinical study with a prespecified statistical analysis plan comparing the pharmacokinetics, pharmacodynamics, safety, and immunogenicity of two prescription drugs products."[iv] This update may be particularly relevant for oncology and rare disease products where a confirmatory Phase II trial may be deemed sufficient evidence to support accelerated approval. Furthermore, the Final SIUU Guidance allows that certain other

studies – such as meta-analyses, cohort or case-control studies, open-label studies, single-arm studies, externally controlled trials, and observational studies – could also meet the scientifically sound standard.[v]

ADDITIONAL NOTEWORTHY UPDATES ON PRESENTATION OF SIUU

Both the 2023 Draft Guidance and the Final SIUU Guidance include several recommendations for presenting SIUU. The key recommendations from the 2023 Draft Guidance regarding presentation remain in the Final SIUU Guidance, including clearly and prominently presenting disclosures, separating SIUU communications from promotional communications, and selecting platforms that allow dissemination of SIUU in a manner consistent with the guidance. Notable differences in the Final SIUU Guidance include the following:

- **Removal of the "plain language" recommendation for firm-generated presentations:** The Final SIUU Guidance entirely omits the recommendation from the 2023 Draft Guidance to present firm generated presentations in "plain language." This update is helpful as the "plain language" recommendation arguably contradicted other language in the 2023 Draft Guidance suggesting that firms should closely adhere to the information as presented in the SIUU source document.
- **Additional guidance on delivery methods, including in-person delivery**: Like the 2023 Draft Guidance, the Final SIUU Guidance blesses a variety of distribution methods, including conference booths, websites, email, and other print and digital media. One notable addition in the Final SIUU Guidance is a new example specific to in-person delivery by firm representatives. While in-person delivery was implied in the 2023 Draft Guidance, the Final SIUU Guidance provides further clarity on FDA's thinking about the recommended training and expertise of those delivering SIUU. Firm representatives who share SIUU communications should have "specialized training in providing truthful, non-misleading scientific information about unapproved uses" and should also be trained to handle potential questions or "know how to direct the questions to personnel qualified to respond (e.g., medical or scientific / technical representative or department)."[vi] Even with this additional language, *how* to execute in-person delivery of SIUU will likely continue to be a hot topic for firms developing SIUU communication strategies and SOPs, particularly since the Final SIUU Guidance also contemplates that SIUU and promotional communications might be shared during the same in-person visit.
- **Clarification of FDA's views on "persuasive marketing techniques" in SIUU communications:** The 2023 Draft Guidance cautioned firms against using "persuasive marketing techniques" in SIUU communications. While the Final SIUU guidance removes use of the term "persuasive marketing techniques," it maintains the general principle that firms should not use communication techniques that encourage an unapproved use based on elements other than the scientific content.[vii] In the 2023 Draft Guidance, FDA listed celebrity endorsements, premium offers, and gifts as examples of persuasive marketing techniques. The Final SIUU Guidance provides the following additional examples:[viii]
    - Jingles
    - Emotional appeals unrelated to the scientific content (*e.g.*, statements such as "Don't give up hope for your patients" and inspirational images such as a sunrise, a joyful family gathering, or a basket of puppies)
    - Promotional tag lines (*e.g.*, "Nothing but the BEST from [Medical product X].")

  The Final SIUU Guidance also cautions against "calls to value" that pre-judge the benefit(s) of the medical product for individual patients (e.g., "Call FIRM X now for more information on [Medical Product X] – it's the best option for your difficult-to-treat patients" or "Click here to start improving your patients' lives today").[ix] Instead, FDA recommends a factual call to action focused on access to the scientific information without a promotional

claim, value judgment, or implication of benefit, such as “Click here to access the full article for free” or “Read now to learn more about this data for Medical Product X.” The intent of SIUU should be information exchange and not persuading or convincing an HCP to prescribe a product for an unapproved use.[x]

NOTEWORTHY UPDATE ON FDA’S FIRST AMENDMENT POLICY

In addition to publishing the Final SIUU Guidance, FDA contemporaneously updated key policy documents explaining the Agency’s First Amendment position and premarket review processes. Without fanfare, footnote 9 of the Final SIUU Guidance refers and links to addenda for FDA’s First Amendment Memorandum and Summary of Premarket Review, both originally issued in January 2017 alongside draft guidances for CFL and payor communications.[xi] Updates to these materials reflect the Agency’s careful consideration and defense of the Final SIUU Guidance in light of the First Amendment and Agency processes.

CONCLUSION

In general, the Final SIUU Guidance remains consistent with the 2023 Draft Guidance in terms of general principles. However, firms that currently develop and distribute SIUU communications will need to analyze the updated aspects of the Final SIUU Guidance and consider how those differences may impact their current approach to SIUU communications. We have worked closely with both large and small pharmaceutical and medical device companies to evaluate and implement the guidance over the past year, including conducting training workshops, developing template presentation materials, and reviewing draft SIUU materials. We are poised to provide similar guidance to clients interested in implementing SIUU communications for the first time, or those needing to update current practices and materials to address the changes in the Final SIUU Guidance.

WEBINAR ON FINAL SIUU GUIDANCE: JANUARY 29

On January 29, we will host a one-hour webinar to further discuss the Final SIUU Guidance. In addition to key differences between the draft and final guidance and important implementation considerations, the webinar will also discuss FDA’s stated position on SIUU in light of the First Amendment. Webinar registration will open soon.

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[i] For an overview of the draft version of this guidance, see Client Alert, Beyond Reprints for Scientific Information on Unapproved Uses of Medical Products (October 25, 2023). The 2023 Draft Guidance superseded the Agency’s 2014 Revised Draft Guidance, Distributing Scientific and Medical Publications on Unapproved New Uses – Recommended Practices (hereinafter, 2014 Revised Draft Reprints Guidance). Our Client Alert on the 2023 Draft Guidance provided both an overview of the document at the time and a comparison to the 2014 Revised Draft Guidance.

[ii] “Scientifically sound” was the evidentiary standard used in the 2014 Revised Draft Reprints Guidance.

[iii] *See* 2023 Draft Guidance at 11-12. ("Such scientific data generated in early stages of product development are unlikely to be sufficiently reliable by themselves to allow for a determination of clinical relevance.")
[iv] *See* Final SIUU Guidance at 13.
[v] *Id.*
[vi] *Id.* at 19, note 49.
[vii] *Id.* at 26-27.
[viii] *Id.* at 27.
[ix] *Id.*
[x] *Id.* at 27-28.
[xi] *Id.* at 4, note 9. The Final SIUU Guidance cites to (1) a new Addendum to FDA Memorandum, Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products (January 2017) — Additional and Updated Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products (January 2025) (available at https://www.regulations.gov/docket/FDA-2016-N-1149) and (2) a new FDA Summary of Premarket Review and Related Authorities for Medical Products (January 2025) that updates Appendix A of the January 2017 Memorandum and provides an overview of legal authorities governing firms' communications regarding unapproved uses of medical products, including a discussion of the premarket review processes for each type of medical product (available at https://www.regulations.gov/docket/FDA-2016-N-1149). The original 2017 materials were issued in conjunction with the 2017 publication of draft guidance documents, "Medical Product Communications That Are Consistent With the FDA-Required Labeling" (CFL) and "Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities," both of which were later finalized in 2018.