Published on *The National Law Review* https://www.natlawreview.com

# Sharing Scientific Information with HCPs on Unapproved Uses of Medical Products: Dos and Don'ts Under FDA's New Draft Guidance

Article By:

Amy K. Dow

Bonnie Odom

Olivia K. Plinio

In October 2023, the FDA released draft guidance entitled "Communications From Firms to Health Care Providers Regarding Scientific Information on Unapproved Uses of Approved/Cleared Medical Products: Questions and Answers Guidance for Industry" ("2023 Draft Guidance").[1] The 2023 Draft Guidance supersedes previous draft guidance from 2014 entitled "Distributing Scientific and Medical Publications on Unapproved New Uses–Recommended Practices" ("2014 Draft Guidance"), which was a revision of a 2009 final guidance entitled "Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices."

All three of these FDA guidance documents provide recommendations for industry regarding the sharing of scientific information with Health Care Providers ("HCPs")[2] on unapproved uses of approved or cleared drugs and medical devices, termed "SIUU communications" by the 2023 Draft Guidance. HCPs are permitted to prescribe medical products for

unapproved uses when the unapproved use is determined to be medically appropriate for a given patient. However, manufacturers may not promote their products for an unapproved use. For this reason, FDA's position (which is articulated to some extent across all of the above-mentioned guidance documents, but most clearly and emphatically in the 2023 Draft Guidance) is that firm[3] communications to HCPs regarding unapproved uses of approved or cleared products should include all of the information necessary for HCPs to evaluate the strengths, weaknesses, validity, and utility of the information about the unapproved use in order to make determinations regarding medical appropriateness.

In the 2023 Draft Guidance, FDA seeks to balance the interests of HCPs in learning, and manufacturers in sharing, truthful and non-misleading information about unapproved uses of approved medical products, with the intent to inform clinical practice decisions against the government's interest in protecting patients from medical product uses that have not met applicable safety and effectiveness standards required under FDA's premarket approval framework.

While the 2023 Draft Guidance reiterates many of the recommendations from the 2014 Draft Guidance, the 2023 Draft Guidance leverages a new "Q&A" format to provide firms with more detailed and specific recommendations, including hypothetical scenarios, around SIUU communications. Below, we restate the four Q&A questions included in the 2023 Draft Guidance and then highlight key aspects of the responses provided by FDA through brief commentary and recommended Dos and Don'ts.

# Q1. What should firms consider when determining whether a source publication is appropriate to serve as

# the basis for an SIUU communication?

According to the 2023 Draft Guidance, any study or analysis described in a source publication that serves as the basis for an SIUU communication should be scientifically sound,[4] and should provide information that is relevant to HCPs engaged in making clinical practice decisions for the care of an individual patient; in other words, these sources should be clinically relevant.[5] While the 2014 Draft Guidance suggested that scientific or medical journal article reprints intended for distribution to HCPs should describe studies that are considered "scientifically sound" by appropriate experts, the 2023 Draft Guidance builds out this standard and provides greater insight into what types of source material would meet (and not meet) the standard.

Do:

- Choose scientifically sound studies that provide clinically relevant information to support your SIUU communications
    - For human and animal drugs, randomized, double-blind, concurrently controlled superiority trials are most likely to provide both scientifically sound and clinically relevant information (though other well-designed and well-conducted studies may also be appropriate)
    - For medical devices,[6] look to well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, reports of significant human experience with a marketed device as sources of scientifically sound and clinically relevant information
- Consider studies with real-world data and associated real-world evidence, which may meet the scientifically sound and clinically

relevant threshold depending on the nature of the data and underlying analyses

Don’t:

- Rely on studies without an adequate control group, isolated case reports, or studies that lack sufficient detail to permit scientific evaluation as the sole basis for an SIUU communication
- Rely on studies with “unreliable” data, even if you include disclaimers noting the limitations (e.g., studies that fail to control for confounding factors or fail to clearly define study endpoints)
- Rely on articles focused on non-clinical studies as the sole basis for an SIUU communication
- Rely on scientific data generated in early stages of medical product development as the sole basis for an SIUU communication, as such data can produce results that are inconsistent with later studies
- Distort studies in SIUU communications or base SIUU communications on publications that distort studies or include fraudulent data
- Continue to share an SIUU communication that is based on a study or analysis that is no longer clinically relevant (ex: subsequent research has established the findings from the study are not reliable)

# Q2. What information should firms include as part of SIUU communications?

Like the 2014 Draft Guidance, the 2023 Draft Guidance emphasizes the importance of providing certain disclosures with SIUU communications to ensure such communications are not misleading and provide all the information necessary for HCPs to interpret the strengths and weaknesses and validity and utility of the information. The recommended disclosures

in the 2023 Draft Guidance are similar to those recommended in the 2014 Draft Guidance, but are more detailed and extensive.

Do:

- Provide a disclosure statement with any SIUU communication, which should include:
    - A statement that the use described in the communication is unapproved and the safety and effectiveness of the medical product for the unapproved use(s) has not been established
    - Disclosure of the FDA approved use of the medical product, including any limitations and contraindication(s) specified by the product's FDA-required labeling[7]
    - Disclosure of any limitations, restrictions, cautions, warnings, or contradictions described in the FDA-required labeling about the unapproved use(s)
    - Disclosure of any serious, life-threatening, or fatal risks posed by the medical product that are relevant to the unapproved use(s) (that are either in the FDA-required labeling or known by the firm and relevant to the unapproved use)
    - Disclosure of any financial relationships between the firm and any authors, editors, or other contributors to the publications in the SIUU communication
    - A copy of the most current FDA-required labeling (or a mechanism for obtaining the labeling)
    - The publication date of any referenced or included publication(s) (if not specified in the publication or citation)
- For an SIUU communication based on a source publication that is primarily focused on a particular scientific study or studies, for each such study where the following information is not included in the publication, provide a description of:
    - All material aspects of study design, methodology, and results
    - All material limitations related to the study design,

methodology, and results
    - Any conclusions from other relevant studies, when applicable, that are contrary to or cast doubt on the results shared, including citations for any such studies

Don’t:

- Omit any risk evaluation and mitigation strategy (REMS) applicable to the medical product (firms should disclose any REMS and should describe the goal(s) of the REMS)

# Q3. What presentational considerations should firms take into account for SIUU communications?

The 2023 Draft Guidance offers a number of presentation-focused recommendations to ensure that SIUU communications are conveyed in a manner that enhances and does not interfere with HCP understanding of the underlying scientific information, and to avoid such SIUU communications being confused with promotional communications about approved uses.

Do:

- Clearly and prominently present all recommended disclosures, considering type size, font style, layout, contrast, graphic design, headlines, spacing, volume, articulation, pace, and any other techniques to achieve emphasis or notice
- For SIUU communications with both audio and visual components, present disclosures in both the audio and in text at the same time using the same/substantially similar language
- Keep SIUU communications (including those relayed via email)

separate and distinct from promotional communications about approved uses of medical products

- Use dedicated vehicles, channels, and venues for sharing SIUU communications that are separate from the vehicles, channels, and venues used for promotional communications about approved uses of medical products. For example -
    - Present SIUU communications on a separate web page from the web page that hosts promotional communications about approved uses
    - At conferences and similar venues, ensure that SIUU communications are clearly identified and distinct from promotional communications about approved uses (e.g., by dividing booth space to allow a dedicated space for SIUU communications)
- Use plain language in the content developed for SIUU communications to facilitate comprehension (i.e., clear and concise language that does not include technical jargon and clearly explains any scientific or technical terms)

Don’t:

- Use persuasive marketing techniques, such as the use of celebrity endorsements, premium offers, and gifts. According to FDA, a firm’s choice to use persuasive marketing techniques suggests an effort to convince the HCP to prescribe or use the product for the unapproved use based on elements *other than* the scientific content of the communication
- Include direct links from web pages that host promotional communications about approved uses to webpages that host SIUU communications
- Utilize platforms with character limits that do not enable the firm to include the recommended disclosures for sharing SIUU communications (however, such platforms could be used to direct an

HCP to an SIUU communication, subject to certain restrictions)

# Q4. What additional recommendations apply to specific types of SIUU communications?

The 2023 Draft Guidance offers additional recommendations related to certain specific types of SIUU communications including journal reprints and clinical reference resources (such as clinical practice guidelines and reference texts). Of note, the 2023 Draft Guidance provides recommendations for a category of SIUU communications that is not specifically addressed in the 2014 Draft Guidance - “firm-generated presentations of scientific information from an accompanying published reprint.”

Discussion of such firm-generated presentations in the 2023 Draft Guidance represents a departure from the 2014 Draft Guidance, which stated that reprints (as well as clinical reference resources) regarding unapproved uses (of cleared or approved medical products) should *not* be “marked, highlighted, summarized, or characterized” by medical product manufacturers to emphasize or promote an unapproved use. The 2023 Draft Guidance provides new flexibility in this regard, expressly acknowledging that firms may develop their own presentations of scientific information from an accompanying reprint provided such presentation is truthful, non-misleading, factual, unbiased, and provides all the information necessary for HCPs to interpret the strengths and weaknesses and validity and utility of the presented information. The 2023 Draft Guidance includes a number of recommendations for firms to follow to prepare and distribute firm-generated presentations of information from an accompanying reprint.

Do:

- Include the full reprint with the firm-generated presentation
- Include the disclosures outlined above in Q2, and clearly disclose what portions of the communication are firm-generated
- Follow the presentational considerations outlined in Q3

Don’t:

- Imply that the study, analysis, or underlying data or information from the reprint(s) represents larger or more-general experience with the medical product than it actually does
- Present information, such as excerpts, quotes, etc., from the reprint(s) out of context, without the information necessary for HCPs to interpret the strengths and weaknesses and validity and utility of the information
- Include representations or suggestions about the safety or effectiveness of the medical product for the unapproved use(s) that are not consistent with the reprint
- Present any conclusions or representations about safety or effectiveness for the unapproved use without expressly attributing such statements to the reprint, and without immediately following such statements with a disclosure of any financial relationships between the firm and any authors, editors, or other contributors to the publications in the SIUU communication
- Use statistical analyses or techniques to indicate clinical significance or validity of a finding not supported by the data or information in the reprint
- Use tables or graphs or other presentational elements to distort or misrepresent the relationships, trends, differences, or changes among the outcomes evaluated in the reprint

# Conclusion

While the 2023 Draft Guidance veers from the 2014 Draft Guidance in

some respects, many of the same principles have been pulled through into the current guidance. As such, a medical product manufacturer who has already implemented the recommendations from the 2014 Draft Guidance should not face too heavy of a lift to adjust its activities to align with the 2023 Draft Guidance. While the landscape has not shifted drastically overall, firms should still closely review the additional detail and clarifications provided by the 2023 Draft Guidance to mitigate potential risk in navigating the often murky regulatory waters of engaging in off-label and pre-approval communications.

ENDNOTES

[1] Comments on the 2023 Draft Guidance are due by December 26, 2023.

[2] The 2023 Draft Guidance only applies to HCPs engaged in making clinical practice decisions for the care of an individual patient. Per the 2023 Draft Guidance, HCPs include physicians, veterinarians, dentists, physician assistants, nurse practitioners, pharmacists, or registered nurses who are licensed or otherwise authorized by law to prescribe, order, administer, or use medical products in a professional capacity. The 2014 Draft Guidance applied to "health care professionals," but the term was not specifically defined.

[3] As defined by the 2023 Draft Guidance, firms are the "persons legally responsible for the labeling of medical products, and includes applicants, sponsors, requestors, manufacturers, packers, and distributors of medical products, and licensees of such persons, and any persons communicating on behalf of these entities."

[4] To be "scientifically sound," at a minimum, studies should meet generally accepted design and other methodological standards for the particular type of study performed, taking into account established

scientific principles and existing scientific knowledge.

[5] Additionally, statistical robustness is generally necessary, though not sufficient, to determine if a study or analysis is appropriate for an SIUU communication. While statistical robustness factors into the rigor of the design and methodology of a study, it does not assure that the study relates to outcomes of clinical relevance to HCPs.

[6] Notably, while the 2014 Draft Guidance stated that journal articles discussing significant non-clinical research *could* fall within FDA's enforcement discretion policy under the guidance, the 2023 Draft Guidance clarifies that, generally, sharing articles focused on non-clinical studies alone would not be consistent with FDA's enforcement discretion policy as a non-clinical study alone is unlikely to provide information that is clinically relevant.

[7] "FDA-required labeling" includes, but is not necessarily limited to, the labeling reviewed and approved by FDA as part of the medical product premarket review process. For a prescription human drug (including biological products), this consists of the FDA-approved prescribing information that meets the requirements of 21 CFR 201.100. For a device, it includes the labeling approved during the review of a premarket approval application or De Novo classification.



National Law Review, Volumess XIII, Number 324