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Scientific Information on Unapproved Uses of Medical Products: FDA's Final Guidance on Firm Communication to Health Care Providers

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The U.S. Food and Drug Administration (FDA) recently announced final guidance for firms in the medical device and product industry titled, "Communications From Firms to Health Care Providers Regarding Scientific Information on Unapproved Uses of Approved/Cleared Medical Products: Questions and Answers." The guidance outlines FDA's enforcement policy on firm-initiated communications of scientific information about unapproved uses of approved or cleared medical products to health care providers (HCPs) engaged in prescribing or administering medical products to individual patients. It finalizes the October 2023 draft, which updated earlier guidance from 2014 and 2009 on distributing scientific and medical publications about unapproved uses. Implementation is pending Office of Management and Budget (OMB) approval of information collection.

As noted in the guidance, a firm's communication about unapproved uses of its approved or cleared medical products could indicate the firm's intended use for the product. Depending on the circumstances, this might demonstrate noncompliance with premarket requirements or result in the product being deemed misbranded or adulterated. However, HCPs may find scientific information on unapproved uses valuable for making clinical decisions for their patients. The January guidance aims to reassure firms that if their communications align with FDA recommendations, FDA will not consider those communications alone as evidence of a new intended use. Additionally, firms will not be required to submit such communications to FDA at the time they share them with HCPs.

Background

The regulation of medical products in the U.S. has been shaped by experiences with significant

public health risks stemming from the use of products not proven to be safe and effective. In response to public health crises, Congress established premarket review frameworks to ensure that: each intended use of a medical product is properly studied, with safety and effectiveness data submitted to FDA for independent evaluation before the product enters the market, as evidence supporting one use does not guarantee the safety or effectiveness of other uses; relying solely on post-market measures, such as enforcement against false or misleading labeling, is insufficient to protect public health, as it fails to prevent harm from unsafe or ineffective treatments.

As such, the Federal Food, Drug, & Cosmetic Act, the Public Health Service Act, and their implementing regulations (FDA Authorities), prohibit the introduction, or causing the introduction, of a medical product that fails to comply with applicable premarket requirements or is otherwise misbranded or adulterated into interstate commerce – this includes medical products intended for an unapproved use, even if that same medical product is approved by FDA for a different use. The intended use of a medical product may be established from its label, labeling, promotional claims, advertising, and any other relevant source. Accordingly, a firm's communications may be considered relevant when establishing whether the medical product is subject to the FDA Authorities and whether a particular statutory or regulatory provision applies to the medical product.

FDA's premarket review process primarily evaluates whether a medical product is safe and effective for specific uses in a defined population. However, after a product is approved or cleared for a specific indication, clinical practice may indicate utility for certain patients who are not part of the defined population. HCPs often prescribe or use approved or cleared medical products for unapproved uses when an HCP determines that such uses are medically appropriate for individual patients, whose needs and characteristics may differ from those of the population studied for the approved use. In such instances, HCPs may be interested in information about an unapproved use of approved or cleared medical products. FDA cautions, however, that patient harm could result from communicating information about those unapproved uses if that information is false, misleading, or fails to provide and appropriately present all the information necessary for HCPs to understand and evaluate the strengths and weaknesses, validity, and clinical utility of the scientific information on any unapproved uses in the communication. Aware of this, FDA has sought to strike a balance between supporting HCPs' interest in having available scientific information about unapproved uses of approved or cleared medical products to inform clinical practice decisions for the care and management of individual patients without undermining other government interests like motivating the development of scientific data on safety and effectiveness, ensuring that FDA-required labeling is accurate and informative, protecting citizens, and others.

Policy

The final guidance provides recommendations addressing considerations for scientific information on unapproved use(s) (SIUU) of approved/cleared medical product communications (referred to throughout FDA's guidance as SIUU communications) to ensure truthfulness, completeness, and clinical utility. If an SIUU communication is consistent with the recommendations provided in the guidance, FDA "does not intend to use the firm's dissemination of such communication standing alone as evidence of the firm's new intended use." Additionally, FDA does not require the firm to submit that SIUU communication to the agency at the time it is initially shared with HCPs.

Including Source Publications in an SIUU Communication

In the guidance, FDA describes source publication as a published reprint, clinical practice guideline (CPG), reference text, or material from a digital clinical practice resource that is included in a firm's

SIUU communication. FDA recommends that these source publications meet the following criteria:

1. Scientific Soundness. To be scientifically sound, the studies or analyses should meet generally accepted design and other methodological standards for the particular type of study or analysis performed (e.g., provide a clear description of the prespecified hypothesis stated and tested, acknowledge and account for potential bias, and otherwise meet generally accepted scientific standards), taking into account established scientific principles.
    1. Statistical rigor is generally necessary, but not sufficient, for a study or analysis to be scientifically sound.
    2. For human and animal drug studies, examples include, but are not limited to, randomized, double-blind, concurrently controlled superiority trials.
    3. For devices, FDA cites to 21 C.F.R. § 860.7 to demonstrate the types of studies, information, and analyses that are considered valid scientific evidence.
2. Relevance of Existing Knowledge. For appropriate inclusions, firms should consider whether existing scientific knowledge has refuted a conclusion from a study described in that source publication or has corrected a long-held misunderstanding that informed a study described in that source publication.
3. Consistency with Study Results. The studies or analyses should align with the prespecified hypothesis or research question from and be supported by the results from the described study or analysis.

Additionally, firms should consider whether a publisher has retracted any SIUU communications due to discovery of misconduct or errors.

Information Included in an SIUU Communication

FDA recommends that all the following information is included in an SIUU communication:

1. 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.
    1. For example, a statement that “[Medical Product X] has not been approved by FDA for use in [Condition Y], and the safety and effectiveness of [Medical Product X] for [Condition Y] has not been established.”
2. A statement disclosing FDA-approved use(s) of the medical product, including any limitations of use specified in FDA-required labeling.
3. A statement disclosing any limitations, restrictions, cautions, warnings, or precautions described in FDA-required labeling about the unapproved use(s).
4. A copy of the most current FDA-required labeling (or a mechanism for obtaining this labeling, as appropriate).
5. A statement describing any contraindication(s) in FDA-required labeling for the medical product.
6. A statement describing any serious, life-threatening, or fatal risks posed by the medical product that are in FDA-required labeling for the medical product or known by the firm and that are relevant to the unapproved use(s).
    1. If a risk evaluation and mitigation strategy (REMS) has been established under 21 U.S.C. § 355-1, the statement should disclose that fact and should describe the goal(s) of the REMS.
7. A statement identifying any authors, editors, or other contributors to publication(s) included in the SIUU communication who were employees of or consultants to or who received

compensation from the firm at the time of writing, editing, or contributing to the publication, to the extent a firm acting reasonably would know of such relationship.

8. In the case of an SIUU communication that includes one or more source publications primarily focused on a particular scientific study or studies, for each such study where the following information is not included in the source publication, provide a description of:
    1. All material aspects of study design, methodology, and results.
    2. All material limitations related to the study design, methodology, and results.
    3. Any conclusions—from other scientifically sound studies that evaluated the same or similar hypotheses or research questions—that conflict with the conclusions from the studies or analyses described in the source publication(s). The citations for any such studies should also be included.
9. The publication date of any referenced or included source publication (if not specified in the source publication or citation.

Presentational Considerations

To help ensure that SIUU communications are conveyed in a manner that enhances and does not interfere with HCP understanding and evaluation of underlying scientific information, FDA recommends that disclosures be:

1. Clearly and prominently presented;
2. Separate from promotional communications about approved uses of medical products; and
3. Shared through media and via platforms that enable firms to implement the recommendations in this guidance.

Reprints

When firms share SIUU communications that include reprints, those reprints should be unaltered and unabridged to avoid introducing bias or result in the omission of material information. Additionally, FDA recommends that articles chosen for reprinting are peer-reviewed by subject-matter experts, generally available through independent distribution channels where periodicals and reprints are sold or are accessible. The articles should be published in a journal managed by an independent organization that has an editorial board composed of subject-matter experts and that has a publicly stated policy regarding the disclosure of conflicts of interest or biases for all authors, contributors, and editors.

Clinical Reference Resources

When a firm shares an SIUU communication that includes one or more sections from a clinical reference resource (e.g., CPGs, reference texts, or materials from digital clinical practice resources), it should ensure that all necessary information is provided to help HCPs evaluate the strengths, weaknesses, validity, and clinical relevance of the scientific information on the unapproved use(s) presented. This may require sharing multiple related or linked sections from the clinical reference resource. Any sections shared must remain unaltered, unabridged, and directly extracted from the original clinical reference resource.

However, because unabridged CPGs or reference texts generally discuss a wide range of topics and medical products, FDA does not expect a firm to include certain statements of disclosure, descriptions of labeling, or the risks that are in FDA-required labeling or are known by the firm and

that are relevant to the unapproved use(s) posed by each of the firm's medical products mentioned in the CPG or reference text. Instead, FDA recommends a more general statement, providing the following example: "*This [CPG/reference text] describes some uses of medical products that are not approved by the FDA, and the safety and effectiveness of any unapproved use(s) have not been established*."

CPG-Specific Recommendations

FDA recommends that, if chosen for inclusion in an SIUU communication, a CPG have all of the following characteristics:

1. The CPG is based on rigorous reviews of the existing evidence conducted according to a clear, established procedure and following a transparent process that minimizes biases and conflicts of interest.
2. The CPG includes ratings of the recommendations to reflect the quality and strength of evidence that supports each recommendation.
3. The CPG is revised when important new evidence warrants modifications of current recommendations.
4. The CPG is generally available through independent distribution channels (e.g., internet sources, book retailers, subscriptions, libraries) where CPGs are sold or are accessible.

FDA stated that, when considering whether a particular CPG should be included in an SIUU communication, the National Academy of Medicine standards for CPG "trustworthiness" is a helpful resource. These standards outline several factors a CPG should have before including it in an SIUU communication, such as knowledgeable development and consideration of important patient subgroups, among others.

Reference Texts and Materials from Digital Practice Resources

FDA recommends that a reference text or material from a digital clinical practice resource have the following characteristics if a firm chooses to include it in an SIUU communication:

1. It is published by an independent publisher that is in the business of publishing scientific or medical educational content;
2. It is published in a manner consistent with current standards for medical content creation and review that are generally accepted by the medical publishing industry and in accordance with any specific peer-review procedures of the publisher;
3. It is authored, edited, and contributed to by experts who have demonstrated expertise in the subject area(s) through education or experience; and
4. It is generally available or sold through independent distribution channels (e.g., internet sources, book retailers, subscriptions, libraries) for medical and scientific educational content.

Firm-Generated Presentations

An SIUU communication that includes a firm-generated presentation should be truthful and not misleading. It should also provide and appropriately present all information necessary for HCPs to understand and evaluate the strengths and weaknesses, validity, and clinical utility of the presented scientific information on any unapproved use. Firm-generated presentations should be consistent with the same recommendations as other presentational sources. It is consistent with the

enforcement policy issued in this guidance for any firm-generated presentations to use presentational elements and other communication techniques to help explain or illustrate the scientific content in an accurate way or to help ensure clear and prominent presentation of the recommended disclosures.

The enforcement policy outlined does *not* extend to firm-generated presentations of scientific information about an unapproved use of the firm's approved or cleared medical product if those presentations include value judgments that preemptively assess a product's benefits for patients.

- Examples of presentations that include value judgments that preemptively assess a product's benefits for patients include "Call FIRM X now for more information on [Medical product X] — it's the best option for your difficult-to-treat patients!" and "Click here to start improving your patients' lives today."
- Examples of presentations that do *not* include value judgments that preemptively assess a product's benefits for patients include "Click here to access the full article for free!" or "Read now to learn more about this new data on Medical product X."

Finally, because an SIUU communication may influence clinical decisions regarding the use of a medical product for an unapproved use — without the safety and effectiveness assurances provided by premarket review — it is essential that the communication be presented carefully. The communication should not lead HCPs to draw conclusions about the safety or effectiveness of the unapproved use that exceed or misrepresent what is supported by the underlying scientific evidence.

Conclusion

In summary, this guidance demonstrates FDA's attempt to strike a balance between two key considerations: (1) HCPs interest in accessible scientific information about unapproved uses of approved or cleared medical products to inform clinical decision-making for individual patient care, and (2) the government's interest in promoting the development and compliance with premarket requirements for medical products. Adhering to these recommendations, firms can avoid promoting unapproved products in ways that could undermine these objectives and result in FDA enforcement actions.

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