Communications From Firms to Health Care Providers Regarding Scientific Information on Unapproved Uses of Approved/Cleared Medical Products
Questions and Answers
Guidance for Industry
DRAFT GUIDANCE

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Communications From Firms to Health Care Providers Regarding Scientific Information on Unapproved Uses of Approved/Cleared Medical Products Questions and Answers Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This revised draft guidance, when finalized, will provide FDA's current thinking on common questions regarding certain communications by *firms* to *health care providers (HCPs)* of scientific information on *unapproved use(s*) (SIUU) of *approved/cleared medical products*.[2] Specifically, this guidance relates to *firms* sharing the following types of communications with *HCPs*:

- Published scientific or medical journal articles (reprints)
- Published clinical reference resources, as follows:
  - Clinical practice guidelines (CPGs)
  - Scientific or medical reference texts (reference texts)
  - Materials from independent clinical practice resources
- Firm-generated presentations of scientific information from an accompanying published reprint

[1] This guidance has been prepared by the Office of Prescription Drug Promotion in the Office of Medical Policy in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, the Center for Veterinary Medicine, and the Office of the Commissioner at the Food and Drug Administration.

[2] The scope of the italicized terms, for the purposes of this guidance, is further explained in section II of this guidance.

These communication types are further described in Q4 of this guidance.

For the purposes of this guidance, these specific types of communications from *firms* to *HCPs* of scientific information on *unapproved uses* of *approved/cleared medical products* in combination with the disclosures recommended in this guidance are referred to as *SIUU communications*. Other communications by *firms* are not specifically addressed by this draft guidance, and we do not intend to convey any views on such communications in issuing this draft guidance.

The Federal Food, Drug, and Cosmetic Act (FD&C Act), the Public Health Service Act (PHS Act), and their implementing regulations (collectively, the FDA Authorities) prohibit, among other things, the introduction (or causing the introduction) into interstate commerce of a medical product that fails to comply with applicable premarket requirements or is otherwise misbranded or adulterated.[3] This prohibition includes introducing (or causing the introduction) into interstate commerce a medical product that is intended for a use that has not been approved or cleared by FDA, even if that same product is approved or cleared for a different use. These premarket requirements further multiple important government interests and distributing *approved/cleared medical products* for *unapproved uses* can undermine these interests.

In certain circumstances, however, *HCPs* may be interested in scientific information about *unapproved uses* of *approved/cleared medical products* to inform clinical practice decisions for the care of an individual patient. In developing this draft guidance, FDA has sought to strike a careful balance between supporting *HCP* 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 advanced by these statutory requirements will be undermined.

In light of those goals, FDA believes it is critical that *SIUU communications* be truthful, non-misleading, factual, and unbiased and provide all information necessary for *HCPs* to interpret the strengths and weaknesses and validity and utility of the information in the *SIUU communication*. In addition, any study or analysis described in a *source publication* that serves as the basis for an *SIUU communication* should be scientifically sound. The study or analysis should also provide information that is relevant to *HCPs* engaged in making clinical practice decisions for the care of an individual patient (as used in this guidance, clinically relevant).[4] The manner of presentation of *SIUU communications* is also critical to consider. This guidance provides recommendations addressing all of these considerations.

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[3] See FDA Memorandum: Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products (January 2017 Memorandum) (available at https://www.regulations.gov/document/FDA-2016-N-1149-0040). Appendix A of that document provides an overview of legal frameworks relevant to firms' communications regarding unapproved uses of medical products, which include provisions directly governing the premarket review processes as well as certain related adulteration and misbranding provisions (collectively, premarket requirements). In addition, we note that, since FDA issued the January 2017 Memorandum, Congress has amended the relevant authorities in certain respects, see, e.g., sections 505G, 502(a), and 502(gg) of the FD&C Act, 21 U.S.C. 355h, 352(a), and 352(gg).

[4] The term *clinically relevant* is further explained in Q1 of this guidance.

If a *firm* shares an *SIUU communication* with *HCPs* in a manner that is consistent with the recommendations in this guidance, FDA does not intend to use such communication standing alone as evidence of a new intended use. For the purposes of this guidance, we refer to this enforcement policy for SIUU communications as "the enforcement policy outlined in this guidance." In addition, we note that this guidance does not describe the only circumstances in which FDA does not intend to consider a *firm's* dissemination of information about an *unapproved use* of its *approved/cleared medical product* to be evidence of the *firm's* intent that the medical product be used for an *unapproved use*. For example, FDA has issued other guidance documents that address circumstances when FDA would not consider a *firm's* dissemination of information regarding an *unapproved use* of its *approved/cleared medical product* to be evidence of intended use.[5] We also note that nothing in this draft guidance is intended to convey new policy regarding a *firm's* existing obligations under the FDA Authorities to update *FDA-required labeling* to accurately reflect what is known about the safety profile of the drug, to ensure that the *FDA-required labeling* is not false or misleading, or for other reasons.[6]

This guidance includes examples to illustrate some of the recommendations and general considerations for *firms* engaged in sharing *SIUU communications* with *HCPs*. The examples in this guidance do not describe every aspect of the *SIUU communication*.

In developing this draft guidance, FDA considered stakeholder feedback from ongoing efforts, including comments received on the guidance entitled *Distributing Scientific and Medical*

[5] FDA issued a draft guidance with recommendations for firms on responding to unsolicited requests for information about unapproved uses of approved medical products (see the draft guidance for industry *Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices* (December 2011)). When final, that guidance will represent FDA's current thinking on this topic. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents. FDA has also provided recommendations for industry support of scientific or educational activities (such as Continuing Medical Education programs) without being subject to FDA regulation (see the guidance *Industry-Supported Scientific and Educational Activities* (December 1997)). In June 2018, FDA issued a final guidance that provides recommendations for firms' communications with payors and similar entities (see the guidance *Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities – Questions and* Answers (June 2018) (superseded in part by section 502(gg) of the FD&C Act enacted in December 2022 as part of the Consolidated Appropriations Act, 2023 (Public Law No. 117-328)). Furthermore, in amending FDA's regulations regarding evidence of intended use in 2020–2021, FDA provided several examples of evidence that, standing alone, are not determinative of intended use. See Proposed Rule (NPRM): Regulations Regarding "Intended Uses" (2020 Intended Use NPRM) (85 FR 59718 at 59725–26, September 23, 2020); Final Rule: Regulations Regarding "Intended Uses" (2021 Intended Use Final Rule) (86 FR 41383, 41397, August 2, 2021). In addition, it 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. (See January 2017 Memorandum (cited in footnote 3 of this guidance) at 20–21).

[6] See, e.g., section 502(a) of the FD&C Act; 21 CFR 201.56(a)(2) ("labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading"), 21 CFR 314.70 and 601.12 (concerning supplements and other changes to an approved application, including labeling), and 21 CFR 514.8(c) (concerning supplements and other changes to an approved application for a new animal drug, including labeling).

Publications on Unapproved New Uses – Recommended Practices (2014 revised draft guidance). This draft guidance will supersede the 2014 revised draft guidance. Changes include a revised title, a question-and-answer format, and certain changes in scope.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. SCOPE

As previously noted, the *SIUU communications* addressed by this draft guidance relate to scientific information on an *unapproved use* of an *approved/cleared medical product.* This is one of several important aspects of the scope of this guidance that are further described in this section. We begin by describing the scope of *unapproved use*, *approved/cleared medical product*, and related terms as those terms are used in this guidance:

- The term *medical product* refers to a medical device for human use (including one that is a biological product), a human drug (including one that is a biological product), or an animal drug.

- The term *approved/cleared medical product*[7] refers only to certain medical products that may be introduced into interstate commerce for at least one use under the FDA Authorities as a result of having satisfied applicable premarket requirements, as follows:

  - With respect to a device, the term refers only to a device that is the subject of an approved premarket application (PMA) under section 515 of the FD&C Act, a 510(k) clearance, or a De Novo classification; to a device that is licensed under PHS Act section 351; or to a device that is exempt from premarket notification.

  - With respect to a human drug, the term refers only to a drug that is the subject of an approved application under section 505 of the FD&C Act or section 351 of the PHS Act, or it is marketed in compliance with section 505G of the FD&C Act.

  - With respect to an animal drug, the term refers only to a drug that is the subject of an approved application under section 512 of the FD&C Act; it does not include a conditionally approved or indexed animal drug.

[7] This term has been chosen for ease of reference within this guidance and its use in this guidance is not intended to indicate that every medical product covered by this term is referred to as "approved" or "cleared" under the language of the FDA Authorities. For example, nonprescription drugs that satisfy requirements for marketing under Section 505G of the FD&C Act are not "approved" under Section 505. The use of the term "approved/cleared medical product" also does not convey that the introduction of the medical product into interstate commerce for an *unapproved use* would be legal.

Note, this guidance does not apply to communications about a use that is an "unapproved use of an approved product" for the purposes of section 564 of the FD&C Act and that is an authorized emergency use under that section (see sections 564(a)(2)(B) and (a)(4)(E) of the FD&C Act).[8]

- The term *approved use*[9] refers to a use that is lawfully included as an indication or use in the *FDA-required labeling* of an approved/cleared medical product (as that term is defined in this guidance) as a result of having satisfied applicable premarket requirements.

- The term *unapproved use* refers to a use that is not lawfully included as an indication or use in the *FDA-required labeling* of an approved/cleared medical product (as that term is defined in this guidance).

- The term *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. FDA-required labeling includes, for example:

  - for a prescription human drug (including a drug that is licensed as a biological product), the FDA-approved prescribing information that meets the requirements of 21 CFR 201.100

  - for a nonprescription human drug that is the subject of an approved drug application under section 505 of the FD&C Act, the FDA-approved Drug Facts labeling that meets the requirements of 21 CFR 201.66

  - for a nonprescription drug that is not the subject of an approved drug application under section 505 of the FD&C Act but instead is marketed under section 505G of the FD&C Act, the labeling that must be provided in order for that drug to comply with section 505G

  - for an animal drug, the FDA-approved prescribing information

  - for a device, the labeling approved during the review of a premarket approval application or De Novo classification

[8] In addition, this guidance does not apply to any communications about a medical product that is an "unapproved product" as that term is used in section 564 of the FD&C Act, including communications about a use that is an authorized emergency use under that section. (See sections 564(a)(2)(A) and (a)(4)(D) of the FD&C Act.)

[9] This term is chosen for ease of reference within this guidance. We note that for certain categories of medical products, the FDA Authorities use terms other than "approved" to describe satisfaction of applicable premarket requirements.

- for a device subject to premarket notification (510(k)) requirements or exempt from premarket review, the labeling that provides indications for use and adequate directions for use and other information required to appear on the label or in labeling

We next describe the meaning, as used in this guidance, of additional key terms that relate to the scope of this draft guidance:

- The term *firm* or *firms* refers to the persons legally responsible for the labeling of medical products, and includes applicants, sponsors, requestors,[10] manufacturers, packers, and distributors of medical products, and licensees of such persons, and any persons communicating on behalf of these entities.

- The term *health care providers* (*HCPs)* refers to individuals such as 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 recommendations in this guidance are specific to communications by firms to HCPs engaged in making clinical practice decisions for the care of an individual patient.[11]

- The term *SIUU communications* refers to specific types of communications (see section I of this guidance) from firms to HCPs of scientific information on unapproved uses of approved/cleared medical products in combination with the disclosures recommended in this guidance. We acknowledge that firms share these communications through different media (e.g., paper, digital). The recommendations in this guidance apply regardless of the medium of the communication. We also acknowledge that firms communicate with other audiences, and we do not intend to convey any views on communications with other audiences in issuing this draft guidance.

- The term *source publication* refers to the published reprint, CPG, reference text, or material from an independent clinical practice resource that serves as the basis of a firm's SIUU communication.

This draft guidance does not cover a firm's communications of scientific information in response to unsolicited requests, which are addressed in the draft guidance for industry *Responding to*

[10] See section 505G(q)(3) of the FD&C Act.

[11] FDA has separate recommendations for a firm's communications with the payor audience, which could include HCPs serving on formulary committees or other entities carrying out responsibilities for medical product selection or acquisition, formulary management, and/or coverage and reimbursement decisions on a population basis (payors). (See the guidance for industry *Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities – Questions and Answers*. See also section 502(a) and (gg) of the FD&C Act, 21 U.S.C. 352(a) and (gg).) Additionally, while HCPs may serve as researchers, a firm's communications with HCPs in their capacities as researchers are not within the scope of this guidance. The Agency is separately soliciting public comment on the topic of a firm's communications with researchers.

Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices (December 2011).[12]

III. BACKGROUND

The evolution of medical product regulation in the United States has been shaped by experience with the real and substantial risks to the public from uses of medical products not shown to be both safe and effective. Congress developed the premarket review frameworks for medical products in response to public health tragedies, realizing that (1) safety and effectiveness for each intended use needs to be appropriately studied by firms and then independently evaluated by FDA before a medical product is introduced into interstate commerce for that use because the evidence that demonstrates effectiveness and safety for one use of a product provides no guarantee of the effectiveness or safety of additional uses; and (2) exclusive reliance on post-market remedies (e.g., enforcement actions for false or misleading labeling) is unacceptable as a public health strategy because it does not prevent consumers from experiencing harm from unsafe and/or ineffective treatments.[13]

Accordingly, the FDA Authorities prohibit the introduction (or causing the introduction) into interstate commerce of a medical product that fails to comply with applicable premarket requirements.[14] This prohibition includes the introduction (or causing the introduction) into interstate commerce of a medical product that is intended for a use that has not been approved (an unapproved use), even if that same medical product is approved by FDA for a different use.[15]

The intended use of a medical product can be established from, among other things, its label, accompanying labeling, promotional claims, advertising, and any other relevant source.[16] For example, claims or statements made by or on behalf of a firm that explicitly or implicitly

[12] When final, that guidance will represent FDA's current thinking on this topic.

[13] See January 2017 Memorandum (cited in footnote 3 of this guidance) at 1, 4, and footnote 8.

[14] For a more detailed discussion of many relevant statutory provisions and implementing regulations related to premarket review of medical products, see Appendix A of the January 2017 Memorandum.

[15] The concept of intended use is fundamental to the regulatory approach for medical products embodied in the FDA Authorities. Intended use is an element in the definitions of *drug* and *device*, helping to define the scope of FDA's authority over medical products and subjecting the medical products to the drug or device provisions of the FDA Authorities, as applicable. In addition, intended use may affect the appropriate premarket review pathway for a medical product and is a separate element in establishing certain violations under the FDA Authorities. (See, generally, 2020 Intended Use NPRM, 85 FR 59718 at 59724; 2021 Intended Use Final Rule, 86 FR 41383 at 41385.)

[16] See, e.g., 2021 Intended Use Final Rule, 86 FR 41383 at 41386-41388 (citing cases).

promote a medical product for a particular use may be taken into account.[17] Accordingly, a firm's communications may be relevant to establishing whether its medical product is subject to the FDA Authorities and whether particular statutory or regulatory provisions apply to the medical product.

The premarket requirements of the FDA Authorities advance substantial government interests that include increasing the availability of medical products that have been shown to be safe and effective for a particular use and in preventing direct and indirect harm from uses of medical products that have not been shown to be safe and effective. Maintaining the premarket review process for safety and effectiveness of each intended use advances these and other interests, including protecting against fraud, misrepresentation, and bias, and preventing the diversion of health care resources toward ineffective treatments.

The premarket requirements of the FDA Authorities advance further substantial government interests, including motivating the development of robust scientific data on safety and effectiveness; ensuring that the FDA-required labeling is accurate and informative; protecting the integrity and reliability of promotional information regarding medical product uses; protecting human subjects receiving experimental treatments; ensuring informed consent; maintaining incentives for clinical trial participation; protecting innovation incentives, including statutory grants of exclusivity; and promoting the development of products for underserved patients.[18]

Generally, FDA's premarket review process focuses on determining whether a medical product is safe and effective for the specified use(s) in an identified population. However, after the premarket review process is complete and a product is approved/cleared, questions may arise in clinical practice relating to the use of the medical product for a particular patient.

HCPs prescribe and use approved/cleared medical products for unapproved uses when they judge that the unapproved use is medically appropriate for their particular patient—whose characteristics and needs may differ from the characteristics of the population(s) reflected in the approved use(s).[19] This practice may be most common in patients with diseases for which there is no medical product that is a proven treatment or in patients who have exhausted all approved uses of medical products.[20] In such instances, HCPs may be interested in communications about unapproved uses of approved/cleared medical products. However, especially because such communications may be used to inform clinical practice decisions for the care of an individual patient, it is critical that these communications be truthful, non-misleading, factual, and unbiased and include all information necessary for HCPs to interpret the strengths and weaknesses and

[17] See, e.g., 21 CFR 201.128 (drugs); 21 CFR 801.4 (devices); 2020 Intended Uses NPRM, 85 FR 59718 at 59721; 2021 Intended Use Final Rule, 86 FR 41383 at 41386–41397, footnote 3.

[18] See January 2017 Memorandum at 3–16.

[19] The extra-label use of approved veterinary or human drugs in animals is permitted only if it complies with section 512(a)(4) and (a)(5) of the FD&C Act, 21 U.S.C. 360b(a)(4) and 360b(a)(5), and 21 CFR part 530.

[20] See January 2017 Memorandum at 17.

validity and utility of the information about the unapproved use. It is also critical that such communications be based on studies and analyses that are scientifically sound and provide clinically relevant information. In contrast, patient harm could result from communicating information about unapproved uses of approved/cleared medical products to HCPs who are engaged in prescribing or administering those medical products to an individual patient if that information is false, misleading, biased, or not based on studies and analyses that are scientifically sound and able to provide clinically relevant information.[21] And where firms choose to use persuasive marketing techniques (as that term is described below) in communications regarding unapproved uses, this suggests an improper intent to market the relevant products for unapproved uses.

Cognizant of all these factors, FDA, in implementing the premarket requirements of the FDA Authorities and, more specifically, in developing this draft guidance, has sought to strike a careful balance, supporting HCP interest in scientific information about unapproved uses of approved/cleared medical products to inform clinical practice decisions for the care of an individual patient, but without undermining the other government interests described elsewhere in this guidance document. This includes the government interest in incentivizing the development of and satisfaction of applicable premarket requirements for medical products, which reduces the need to rely on unapproved use(s), and in protecting patients from medical product uses that have not been shown to be safe and effective.

This draft guidance represents a continuation of FDA's ongoing efforts to consider, develop, and refine its policies and recommendations relating to communications by firms about unapproved uses of their approved/cleared medical products. In 2009, FDA issued the guidance for industry *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* to provide guidance to firms on distributing "journal articles" and "scientific or medical reference publications." Then, FDA issued the 2014 revised draft guidance to clarify the Agency's position on a firm's dissemination of scientific or medical reference texts and CPGs that include information on unapproved uses of the firm's medical products and to provide additional explanation on these topics.

In 2016, FDA held a public hearing and requested comments on the topic of "Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products" (2016 public hearing) (81 FR 60299, September 1, 2016). In response to comments at the hearing, FDA developed and placed in the docket (FDA-2016-N-1149-0040) a memorandum to provide additional background on the issues it is considering as part of its review of its rules and policies relating to communications by firms regarding unapproved uses of approved or cleared medical products. (See FDA Memorandum: Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of

[21] As an example, FDA generally does not consider preliminary scientific data to be clinically relevant because "[w]hen what exists is preliminary scientific data, the ultimate relevance and utility of that data is often unknown. That is, one might truthfully summarize the data generated by a preliminary study without being able to determine whether any inferences or conclusions drawn from the data would ultimately be shown to be correct . . . ." (See January 2017 Memorandum (cited in footnote 3 of this guidance) at 7.)

Approved or Cleared Medical Products (January 2017 Memorandum), cited at footnote 3 of this guidance; see also 82 FR 6367, January 19, 2017 (announcing the addition of the January 2017 Memorandum to the 2016 public hearing docket and extending the comment period).) FDA also revised its intended use regulations, publishing the final rule in 2021. See 2021 Intended Use Final Rule, 86 FR 41383 (August 2, 2021), codified at 21 CFR 201.128 and 801.4. The preambles to the proposed and final rules address some related topics. In addition, the guidance for industry *Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities – Questions and Answers* (June 2018) and subsequent legislation address related topics (see footnote 5 of this guidance).

IV. QUESTIONS AND ANSWERS

Q1. What should firms consider when determining whether a source publication is appropriate to serve as the basis for an SIUU communication?

Source publications that serve as the basis for SIUU communications should describe studies or analyses that are scientifically sound and provide clinically relevant information. To be scientifically sound, the studies or analyses, at a minimum, should meet generally accepted design and other methodological standards for the particular type of study or analysis performed, taking into account established scientific principles and existing scientific knowledge.[22] To be clinically relevant, the studies or analyses, in addition to being scientifically sound, should provide information that is pertinent to HCPs engaged in making clinical practice decisions for the care of an individual patient.

For human and animal drugs, randomized, double-blind, concurrently controlled superiority trials are usually regarded as the most rigorous design and informative to clinical practice, and therefore the most likely to provide scientifically sound and clinically relevant information; however, other well-designed and well-conducted trials are also able to generate scientifically sound and clinically relevant information. For medical devices, the types of studies, information, and analyses that are considered valid scientific evidence are described in 21 CFR 860.7 and may include well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device. For medical devices, these types of studies, information, and analyses are most likely to be scientifically sound and clinically relevant.

Real-world data and associated real-world evidence about medical products may be scientifically sound and clinically relevant depending on the characteristics of the data and the nature of the

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

analyses.[23] Other types of well-designed and well-conducted studies and analyses can also be informative to HCPs, but any study or analysis described in a source publication should be evaluated in light of its limitations to determine whether the study or analysis is scientifically sound and provides clinically relevant information.

Certain studies without an adequate comparison or control group, isolated case reports about medical products, and other reports that lack enough detail to permit scientific evaluation would generally not be scientifically sound or clinically relevant and, therefore, use of such reports alone as the basis for an SIUU communication would not be consistent with the enforcement policy outlined in this guidance.

Similarly, communications that distort studies as well as communications based on publications that distort studies[24] or include fraudulent data would not be consistent with the enforcement policy outlined in this guidance and may also violate provisions of the FDA Authorities, such as section 502(a) of the FD&C Act. In situations where flaws of a study or analysis render the data unreliable,[25] such study or analysis should also be excluded from serving as the basis of an SIUU communication as even full disclosure of the limitations of such study or analysis would not permit interpretation of results or attribution of the results to an effect of the medical product.

Of note, scientific data generated in early stages of medical product development can produce results that are not borne out in later studies, as demonstrated by the failure of some clinical studies[26] to support the use of a medical product for the treatment of a disease or condition for

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[23] For example, analyses of real-world data should be prespecified, protocols and statistical analysis plans should be finalized prior to conducting the prespecified analyses, and data integrity should be carefully monitored and maintained. For more information on considerations relevant to real-world data and real-world evidence, see, for example, the guidance for industry and Food and Drug Administration staff *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices* (August 2017) and the guidance for industry *Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products* (August 2023).

[24] Studies may be distorted by, for example, inaccurately describing or interpreting results.

[25] For example, studies or analyses that fail to control for confounding factors, fail to enroll the appropriate spectrum of patients, or fail to include clear definitions of study endpoints are unlikely to produce reliable results. Additionally, studies or analyses based on, for example, poorly extracted data or data that is transferred with errors, is not source verified, or is inaccurately collected and documented would not provide reliable information. For further discussion of common weaknesses in study design, see, e.g., Appendix D, Common Weaknesses in Study Designs. Institute of Medicine (US) and National Research Council (US) Committee on New Approaches to Early Detection and Diagnosis of Breast Cancer; Joy JE, Penhoet EE, Petitti DB, editors. (2005). *Saving Women's Lives: Strategies for Improving Breast Cancer Detection and Diagnosis*. Washington (DC): National Academies Press (US). Available from https://www.ncbi.nlm.nih.gov/books/NBK22323/.

[26] For example, the failure rate during the process of new prescription drug development exceeds 95 percent (see National Center for Advancing Translational Sciences. About New Therapeutic Uses. U.S. Department of Health and Human Services, National Institutes of Health. Retrieved August 14, 2023, from https://ncats.nih.gov/ntu/about). Similarly, medical devices have a very high failure rate in their first prototype tests, with a reported 90 percent of medical devices failing in their first prototype tests (see Intertek (2010). The Top 10

which the medical product initially appeared promising.[27,28] 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. As a result, a communication based on this type of data alone is unlikely to be within the scope of the enforcement policy outlined in this guidance.

Finally, it would not be consistent with the enforcement policy outlined in this guidance to continue to share an SIUU communication that is based on a study or analysis that is no longer clinically relevant. A study or analysis may no longer be clinically relevant because, for example, subsequent research has established that the findings from the study or analysis are not reliable. Accordingly, when a firm has shared on the internet an SIUU communication that is based on a study or analysis that is later determined to no longer be clinically relevant and the firm has the ability to remove their SIUU communication, we recommend the firm remove their SIUU communication.[29]

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

It is critical that SIUU communications be truthful, non-misleading, factual, and unbiased and provide all information necessary for HCPs to interpret the strengths and weaknesses and validity and utility of the information in the SIUU communication. Accordingly, FDA

Reasons Medical Devices Fail Product Certification Testing the First Time. Available at https://www.intertek.com/medical/10-reasons-medical-devices-fail-testing-paper/).

[27] One report evaluated 22 case studies of drugs, vaccines, and medical devices from 1999 to 2017 in which promising phase 2 clinical trial results were not confirmed in phase 3 clinical trials. Phase 3 studies did not confirm phase 2 findings of effectiveness in 14 cases, safety in 1 case, and both safety and effectiveness in 7 cases. These unexpected results could occur even when the phase 2 study was relatively large and even when the phase 2 trials assessed clinical outcomes. In two cases, the phase 3 studies showed that the experimental product increased the frequency of the problem it was intended to prevent (see U.S. Food and Drug Administration Report. (2017). 22 Case Studies Where Phase 2 and Phase 3 Trials Had Divergent Results. Available at https://www.fda.gov/media/102332/download).

[28] Further study is often needed to demonstrate safety and effectiveness for an intended use because the ultimate relevance and utility of scientific data generated in early stages of product development often cannot be ascertained from that early-stage data alone. See, e.g., Echt DS, Liebson PR, Mitchell LB et al. (1991). Mortality and Morbidity in Patients Receiving Encainide, Flecainide, or Placebo: The Cardiac Arrhythmia Suppression Trial. *New Eng. J. Med*., 324(12): 781-88. The Cardiac Arrhythmia Suppression Trial (CAST) was a well-controlled study that examined the widely held belief (in the absence of well-controlled studies showing this to be true) that treating minor rhythm abnormalities (frequent ventricular premature beats) with anti-arrhythmics after an acute myocardial infarction would improve survival. To test this belief, the National Institutes of Health conducted the CAST study which demonstrated that, although the drugs did indeed treat minor rhythm abnormalities, the patients who took those drugs had a 2 ½ fold increase in mortality. See also National Academy of Sciences (1969), *Drug Efficacy Study: Final Report to the Commissioner of Food and Drugs, Food and Drug Administration*, which found that approximately one-third of all pre-1962 marketed drugs did not have a single effective use.

[29] While it would not be consistent with the enforcement policy outlined in this guidance for a firm to continue to share a communication based solely on a study or analysis that is no longer clinically relevant, a communication that includes some discussion of or reference to a source publication containing historical information, such as to describe the historical context and evolution of clinical knowledge in a subject area, would be consistent with the recommendations of this guidance if it makes clear that the historical information is no longer clinically relevant.

recommends that firms include all of the following information as part of SIUU communications:[30]

- 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
  - 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."
- A statement disclosing the FDA-approved use(s) of the medical product, including any limitations of use specified in the FDA-required labeling
- A statement disclosing any limitations, restrictions, cautions, or warnings described in the FDA-required labeling about the unapproved use(s)
- A copy of the most current FDA-required labeling (or a mechanism for obtaining this labeling, as appropriate)
- A statement describing any contraindication(s) in the FDA-required labeling for the medical product
- A statement describing any serious, life-threatening, or fatal risks posed by the medical product that are in the FDA-required labeling for the medical product or known by the firm and that are relevant to the unapproved use(s)[31]
- 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[32] at the time of writing, editing, or contributing to the publication, to the extent a firm acting reasonably would know of such relationship

[30] See item 2 in Q4 of this guidance for information on limited exceptions to the recommendations in this section when SIUU communications in the form of certain unabridged CPGs or reference texts in their entirety are shared.

[31] 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.

[32] Systematic reviews of studies funded and/or conducted by the firm or its representatives demonstrate bias favoring a firm's medical product. See, e.g., Lexchin, J., Bero, L. A., Djulbegovic, B., & Clark, O. (2003). Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ (Clinical research ed.)*, *326*(7400), 1167–1170. https://doi.org/10.1136/bmj.326.7400.1167 (reviewing 30 studies finding that "[s]ystematic bias favours products which are made by the company funding the research."); Lundh, A., Lexchin, J., Mintzes, B., Schroll, J. B., & Bero, L. (2017). Industry sponsorship and research outcome. *The Cochrane database of systematic reviews*, *2*(2), MR000033. https://doi.org/10.1002/14651858.MR000033.pub3 (reviewing 48 studies

- In the case of an SIUU communication that is based on a source publication that is primarily focused on a particular scientific study or studies,[33] for each such study[34] where the following information is not included in the publication, provide a description of:[35]
  - All material aspects of study design, methodology, and results
  - All material limitations related to the study design, methodology, and results[36]
  - 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
- The publication date of any referenced or included publication(s) (if not specified in the publication or citation)

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

As noted above, the premarket requirements of the FDA Authorities further multiple important government interests. In developing this draft guidance, FDA has sought to strike a careful balance between supporting HCP 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 advanced by these statutory requirements will be undermined. There are several presentational considerations that can help achieve the appropriate balance, in part by helping to ensure that SIUU communications are conveyed in a manner that enhances and does not interfere with HCP understanding and evaluation of the underlying scientific information, including its limitations. In addition to the information being truthful and non-misleading, it is critical that the presentation is factual and unbiased. To that end, FDA recommends the following:

1. SIUU communications should clearly and prominently present all disclosures recommended in this guidance.

All recommended disclosures should be clearly and prominently presented. This helps to ensure that HCPs have the information necessary to interpret the scientific information and the SIUU

showing that "[s]ponsorship of drug and device studies by the manufacturing company leads to more favorable results and conclusions than sponsorship by other sources").

[33] FDA anticipates that most SIUU communications of CPGs or reference texts would not be subject to this recommendation because they are not focused primarily on a specific study or studies.

[34] For example, if an SIUU communication includes a reprint that describes two studies in detail, this recommendation applies to each study, even if the SIUU communication does not address them in identical detail.

[35] See item 3 in Q4 for specific recommendations for the presentation of such material information in firm-generated presentations of scientific information from an accompanying reprint.

[36] See Q1 for further discussion of limitations of studies and analyses.

communication as a whole. Factors FDA considers when determining whether information is clearly and prominently presented may include type size, font style, layout, contrast, graphic design, headlines, spacing, volume, articulation, pace, and any other techniques to achieve emphasis or notice.[37] For SIUU communications that have both audio and visual components, to help HCPs notice and comprehend the information, FDA recommends that disclosures be presented in both the audio and in text at the same time using the same words (key terms and phrases or a full transcript).[38] Note, for SIUU communications that have both audio and visual components, it would be consistent with the disclosure recommendations of this guidance for both the audio and visual components to include a statement about how to obtain a copy of the most current FDA-required labeling for the medical product that is the subject of the SIUU communication.

2. SIUU communications should not use persuasive marketing techniques.

When communicating about the approved uses of their medical products, firms often use marketing techniques to influence the views of their audience. Some of these marketing techniques influence use of the products based on elements other than the scientific content of the communication (as used herein, "persuasive marketing techniques"). Examples of these persuasive marketing techniques include the use of celebrity endorsements, premium offers, and gifts.[39] In the context of a firm's communications to HCPs in support of an **unapproved use**, 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, and FDA therefore considers such communications to be evidence of an intended use of the product for purposes of relevant requirements of the FDA Authorities.[40] And because such communications attempt to influence HCPs to reach positive conclusions about the unapproved use based on elements other than the scientific content, such communications are outside the scope of the enforcement policy outlined in this guidance.

[37] FDA assesses disclosure clarity and prominence on a case-by-case basis.

[38] For example, if a firm posts a reprint on a web page and also includes a firm-generated video presentation of scientific information from the accompanying reprint on that web page (see item 3 in Q4), the firm should present recommended disclosures in the video in both the audio and in text at the same time, using the same words.

[39] See, e.g., Datta, A., & Dave, D. (2017). Effects of physician-directed pharmaceutical promotion on prescription behaviors: longitudinal evidence. *Health economics*, *26*(4), 450-468; Meffert, J. (2009). Key opinion leaders: where they come from and how that affects the drugs you prescribe. *Dermatol Ther*, 22, 262-268; Naylor, C., Chen, E., Strauss, B. (1992). Measured enthusiasm: does the method of reporting trial results alter perceptions of therapeutic effectiveness? *Ann Intern Med*. 117(11): 916-21; Price, S., O'Donoghue, A., Rizzo, L., Sapru, S., Aikin, K. (2021). What influences healthcare providers' prescribing decisions? Results from a national survey. *Research in Social and Administrative Pharmacy*, 17(10), 1770-1779; Sismondo, S. (2015). How to make opinion leaders and influence people. *CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne*, 187(10), 759–760.

[40] See 2021 Intended Use Final Rule, 86 FR at 41388 ("Courts have repeatedly held that . . . promotional claims are one source of evidence of intended use").

Because an SIUU communication may be used to inform clinical practice decisions about whether to use an approved/cleared medical product for an unapproved use in an individual patient, it is also important that the communication be presented in a manner that is unlikely to lead HCPs to base those decisions on conclusions about the safety or effectiveness of the unapproved use that are not in alignment with, or that go beyond what is justified by, the underlying scientific information.[41] Research demonstrates that promotional communications about medical products often employ marketing techniques that are effective at influencing attitudes and behaviors of HCPs,[42] and that how information is presented can impact HCP impressions of that information.[43] These marketing techniques can influence attitudes and behavior, independent of the quality of the information, even among highly educated medical professionals.[44]

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[41] See, e.g., Eguale, T., Buckeridge, D. L., Verma, A., Winslade, N. E., Benedetti, A., Hanley, J. A., & Tamblyn, R. (2016). Association of Off-label Drug Use and Adverse Drug Events in an Adult Population. *JAMA internal medicine*, *176*(1), 55–63; Radley, D. C., Finkelstein, S. N., & Stafford, R. S. (2006). Off-label prescribing among office-based physicians. *Archives of internal medicine*, *166*(9), 1021–1026. See also the January 2017 Memorandum at 13 ("Marketing activities and communications regarding the safety and effectiveness of a medical product for a particular use that are not properly supported by scientific evidence may thus create a false or misleading impression about the safety and efficacy of the medical product for that use, which can lead to prescribing or use decisions that harm patients. Examples of some marketing activities that caused such harm are described in Appendix C.").

[42] See e.g., Austad, K. E., Avorn, J., & Kesselheim, A. S. (2011). Medical students' exposure to and attitudes about the pharmaceutical industry: a systematic review. *PLoS Med*, 8(5), e1001037; Austad, K. E., Avorn, J., Franklin, J. M., Campbell, E. G., & Kesselheim, A. S. (2014). Association of Marketing Interactions With Medical Trainees' Knowledge About Evidence-Based Prescribing: Results From a National Survey. *JAMA Internal Medicine*, 174(8):1283-1290; Avorn, J., Chen, M., & Hartley, R. (1982). Scientific versus commercial sources of influence on the prescribing behavior of physicians. *The American Journal of Medicine, 73*(1), 4-8; and Spurling, G. K., Mansfield, P. R., Montgomery, B. D., Lexchin, J., Doust, J., Othman, N., & Vitry, A. I. (2010). Information from pharmaceutical companies and the quality, quantity, and cost of physicians' prescribing: A systematic review. *PLoS Med, 7*(10), e1000352.

[43] See, e.g., Bobbio, M., Demichelis, B., & Giustetto, G. (1994). Completeness of reporting trial results: effect on physicians' willingness to prescribe. *Lancet,* 343(8907), 1209–1211; Bucher, H. C., Weinbacher, M., & Gyr, K. (1994). Influence of method of reporting study results on decision of physicians to prescribe drugs to lower cholesterol concentration. *BMJ (Clinical research ed.)*, 309(6957), 761–764; Kahwati, L., Carmody, D., Berkman, N., Sullivan, H. W., Aikin, K. J., & DeFrank, J. (2017). Prescribers' knowledge and skills for interpreting research results: a systematic review. *The Journal of Continuing Education in the Health Professions*, *37*(2), 129–136; Marcatto, F., Rolison, J.J., & Ferrante, D. (2013). Communicating clinical trial outcomes: effects of presentation method on physicians' evaluations of new treatments. *Judgment and Decision Making*, 8(1), 29-33.

[44] See e.g., Chaiken, S., Liberman, A., & Eagly, A.E. (1980). Heuristic and systematic information processing within and beyond the persuasion context. In *Unintended Thought* (ed. J.E. Uleman). New York: Guilford Press, 212-252; DeJong, C., Aguilar, T., Tseng, C-W., Lin, GA., Boscardin, WJ., Dudley, RA. (2016). Pharmaceutical industry–sponsored meals and physician prescribing patterns for Medicare beneficiaries. *JAMA Intern Med.*, 176(8):1114-1122; Hadland, SE., Cerdá, M., Li, Y., Krieger, MS., Marshall, BDL. (2018). Association of pharmaceutical industry marketing of opioid products to physicians with subsequent opioid prescribing. *JAMA Intern Med*., 178(6):861-863; Inoue, K., Tsugawa, Y., Mangione, CM., Duru, OK. (2021). Association between industry payments and prescriptions of long-acting insulin: An observational study with propensity score Matching. *PloS Med,* 18(6): e1003645; Petty, R. E. & Cacioppo, J. T. (1986); *Communication and Persuasion: Central and Peripheral Routes to Attitude Change.* New York: Springer-Verlag; Sah, S., & Fugh-Berman, A. (2013). Physicians

As explained above, this guidance strives to balance (1) HCP 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 (2) the various government interests in incentivizing the development of and satisfaction of applicable premarket requirements for medical products. A firm's use of persuasive marketing techniques in communications that support unapproved uses does not appropriately serve the purpose of informing clinical practice decisions for individual patient care and therefore does not counterbalance the important government interests discussed above. For these reasons, a firm's communications that support unapproved uses and use persuasive marketing techniques are outside the scope of the enforcement policy outlined in this guidance.

3. SIUU communications should be separate and distinct from promotional communications about approved uses of medical products.

As set forth in this guidance, the medical products that are discussed in SIUU communications are approved/cleared for at least one use, and, as such, it is likely that firms regularly disseminate promotional communications for those approved uses. However, including information about unapproved uses in those promotional communications has the potential to undermine the government interests in the premarket requirements of the FDA Authorities. In this guidance, FDA has sought to strike a careful balance, supporting HCPs interested in scientific information about unapproved uses of approved/cleared medical products to inform clinical practice decisions for the care of an individual patient, while mitigating the potential that the government interests advanced by these statutory requirements will be undermined. To preserve this balance and to avoid misleading HCPs, we strongly recommend that firms avoid sharing an SIUU communication for a medical product together with a promotional communication for that product for its approved use(s) because combining these two types of communications is more likely to lead to conflation of the approved use and unapproved use information.[45] This conflation may lead HCPs to conclude that the firm's medical product has been demonstrated to be safe and effective for all presented uses, including the unapproved use(s), or to conclude that all presented uses of the medical product are uses for which it may be approved/cleared.

Additionally, FDA recommends that firms 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 to reduce the risk of

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under the influence: social psychology and industry marketing strategies. *The Journal of law, medicine & ethics: a journal of the American Society of Law, Medicine & Ethics*, *41*(3), 665–672; Yeh, JS., Franklin, JM., Avorn, J., Landon, J., Kesselheim, AS. (2016). Association of industry payments to physicians with the prescribing of brand-name statins in Massachusetts. *JAMA Intern Med*., 176(6):763-768.

[45] Research indicates that combining multiple communications can prompt conflation of the messages conveyed by each communication. See, e.g., Sullivan, H. W., O'Donoghue, A. C., Rupert, D. J., Willoughby, J. F., Amoozegar, J. B., & Aikin, K. J. (2016). Are Disease Awareness Links on Prescription Drug Websites Misleading? A Randomized Study. *Journal of health communication*, *21*(11), 1198–1207; Aikin, K. J., Sullivan, H. W., & Betts, K. R. (2016). Disease Information in Direct-to-Consumer Prescription Drug Print Ads. Journal of health communication, *21*(2), 228–239.

HCPs conflating the approved and unapproved use information. In cases where there is only one vehicle, venue, or channel available for the sharing of information, a firm should ensure that SIUU communications are clearly identified and distinct from promotional communications about approved uses.

For example, firms may be interested in sharing information about both the approved and unapproved uses of their medical products online through websites. In these cases, FDA recommends that SIUU communications be on a separate web page from the web page that hosts promotional communications about the approved uses of the medical product. FDA also recommends that firms not include direct links from web pages that host promotional communications about approved uses to webpages that host SIUU communications. Similarly, FDA recommends that email messages used to share SIUU communications be separate and distinct from email messages used to share promotional communications about approved uses of the medical product.

Medical or scientific conferences also represent a venue where information about both approved and unapproved uses of medical products is shared. Although conference organizers generally select the content to be shared for the planned sessions and presentations at the conference (e.g., poster sessions),[46] these same conferences also offer venues (e.g., booths in commercial exhibit halls) where firms can independently select and share information with conference attendees, which could include both promotional communications about approved uses of medical products and SIUU communications. When sharing information in commercial exhibit halls and similar venues where programming is not selected and determined by the conference organizers, firms should ensure that SIUU communications are clearly identified and distinct from promotional communications about approved uses.[47] For example, in commercial exhibit halls, FDA strongly recommends that firms divide booth space to allow for a dedicated space where SIUU communications can be shared, separate and distinct from promotional communications about approved uses.

4. SIUU communications should be shared through media and via platforms that enable firms to implement the recommendations in this guidance.

Different media types and platforms are available to firms interested in sharing SIUU communications, and each medium and platform may prompt unique presentational challenges and considerations. For example, certain online platforms may impose character-space

[46] FDA does not consider a firm's presentation of truthful and non-misleading scientific information about unapproved uses in the planned sessions and presentations selected by conference organizers 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.

[47] This recommendation applies even to those SIUU communications that include the same substantive content as presented in planned sessions at the conference. Courts have recognized that a different level of First Amendment scrutiny can apply to the same speech depending on how the speech is communicated. See, e.g., *Washington Legal Foundation* v. *Friedman*, 13 F. Supp. 2d 51, 64 (D.D.C. 1998), *vacated in part sub nom. Washington Legal Foundation v. Henney,* 202 F.3d 331, 336-37 (D.C. Cir. 2000).

limitations or other presentational limitations that would not enable a firm to include within their communications on that platform all of the disclosures that are recommended for an SIUU communication. To be consistent with the recommendations in this guidance, such platforms should not be used to host SIUU communications but could be used to direct HCPs to an SIUU communication. For example, it would be consistent with the recommendations in this guidance for a communication on a character-space limited platform to direct HCPs to an SIUU communication through a statement that does not mention the name of any specific medical product, such as "New publication for Health Care Providers—phase 3 trial results for an investigational treatment for [disease X]," followed by a link to a website where the SIUU communication appears.

Firms should carefully consider the limitations of different media types and platforms to ensure that the medium and platform used for sharing an SIUU communication allows the firm to include all information consistent with the recommendations in this guidance.

5. Firms should consider using plain language in the content they develop for SIUU communications to facilitate comprehension.

Although HCPs have specialized training and experience in evaluating scientific information, research indicates that HCPs may nonetheless have difficulty understanding some types of scientific information, including clinical trial data, and the design and methodological limitations of studies.[48] To aid in comprehension and encourage careful consideration of the information shared in an SIUU communication, firms should consider using plain language for any firm-generated portions of the SIUU communication, including recommended disclosures. Plain language is language that is clear, concise, well-organized, and where possible, avoids complexities such as technical jargon, passive voice, and long sentences and paragraphs.[49] Clearly explaining scientific or technical terms and avoiding or appropriately introducing acronyms and abbreviations can facilitate comprehension.

[48] See, e.g., Anderson, B.L., Schulkin, J. (2014). *Numerical Reasoning in Judgments and Decision Making about Health*. Cambridge University Press; Kahwati, L., Carmody, D., Berkman, N., Sullivan, H. W., Aikin, K. J., & DeFrank, J. (2017). Prescribers' Knowledge and Skills for Interpreting Research Results: A Systematic Review. *The Journal of Continuing Education in the Health Professions*, *37*(2), 129–136; Moynihan, C. K., Burke, P. A., Evans, S. A., O'Donoghue, A. C., & Sullivan, H. W. (2018). Physicians' Understanding of Clinical Trial Data in Professional Prescription Drug Promotion *Journal of the American Board of Family Medicine. JABFM*, *31*(4), 645–649; Weir, I. R., Marshall, G. D., Schneider, J. I., Sherer, J. A., Lord, E. M., Gyawali, B., Paasche-Orlow, M. K., Benjamin, E. J., & Trinquart, L. (2019). Interpretation of time-to-event outcomes in randomized trials: an online randomized experiment. *Annals of oncology: official journal of the European Society for Medical Oncology*, *30*(1), 96–102.

[49] See the U.S. General Services Administration (GSA) Plain Language Action and Information Network (PLAIN) website at https://www.plainlanguage.gov/.

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

This draft guidance addresses a number of different types of SIUU communications. This section offers specific recommendations for firms to take into account for these different types of SIUU communications, in addition to the recommendations outlined in Q1, Q2, and Q3.

1. Reprints:

In this guidance, we use the term *reprint* to refer to a copy of an article originally published by a medical or scientific journal. When firms share SIUU communications in the form of a reprint, FDA recommends that the reprint have all of the following characteristics:

- The article is published in a journal managed by an independent organization with an editorial board comprised of persons who have demonstrated expertise in the subject of the articles under review by the organization (through education or experience), and a publicly stated policy regarding the disclosure of conflicts of interest or biases for all authors, contributors, or editors

- The article is peer-reviewed by experts in the subject of the article, as established by education or experience

- The article is generally available (or the journal from which the article is taken is generally available) through independent distribution channels (e.g., internet sources, book retailers, subscriptions, libraries) where periodicals and reprints are sold or are accessible

- The article describes studies or analyses that are scientifically sound and provide information that is clinically relevant (see Q1); specifically:

  - To be scientifically sound, the scientific studies or analyses described in the article should meet generally acceptable design and other methodological standards for the type of study or analysis being performed (e.g., provide a clear description of the hypothesis stated and tested, acknowledge and account for potential bias, and otherwise meet generally accepted scientific standards for the type of study or analysis performed). Meta-analyses, cohort or case-control studies, open-label studies, single-arm studies, or epidemiological studies can be scientifically sound if these studies and analyses meet generally acceptable design and other methodological standards for the type of study or analysis being performed and take into account any limitations of the selected design and methodology. For some devices, well-documented case histories conducted by qualified experts may also be scientifically sound and provide information that is clinically relevant.

  - To be clinically relevant, the scientific studies or analyses described in the article should, in addition to being scientifically sound, provide information that is pertinent to HCPs engaged in making clinical practice decisions for the care of an individual

patient. Generally, sharing articles focused on a nonclinical study or analysis alone would not be consistent with the enforcement policy outlined in this guidance because this nonclinical study or analysis alone is unlikely to provide information that is clinically relevant.

- Articles that misrepresent or overstate findings in light of the limitations of the study or analysis would not be consistent with the enforcement policy outlined in this guidance.

- Reprints should be unaltered/unabridged as the sharing of unaltered/unabridged articles is less likely to introduce bias or result in the omission of material information.[50]

2. Clinical Reference Resources:

In this draft guidance, we address the following clinical reference resources:

- Clinical Practice Guidelines (CPGs):
  - In this guidance, we use the term *CPG* to refer to a statement or document from a professional or academic organization that includes recommendations focused on a specific disease or condition intended to help HCPs make decisions for individual patient care, including decisions in circumstances where there are few or no approved/cleared medical products indicated for the patient's condition or the approved/cleared medical products have not proven successful for the individual patient.[51]

- Reference Texts:
  - In this guidance, we use the term *reference text* to refer to medical or scientific textbooks that typically discuss a wide range of topics (e.g., medical diagnosis, pathophysiology and treatments, pharmacology, surgical techniques, and other scientific or medical information).

- Materials from Independent Clinical Practice Resources:
  - In this guidance, we use the term *independent clinical practice resource* to refer to a digital resource that contains medical and scientific information on a wide

[50] A firm could develop a truthful, non-misleading, factual, and unbiased presentation of scientific information from an accompanying reprint and not be inconsistent with this recommendation. See item 3 in Q4 for recommendations regarding firm-generated presentations of scientific information from an accompanying reprint.

[51] CPGs can provide a resource for HCPs who may not have the time or capacity to review the full range of primary source publications and make an independent, evidence-based assessment to inform their clinical practice decisions. CPGs provide recommendations for care for a disease or condition, in addition to offering potential alternatives for certain patient subgroups.

range of topics developed by subject matter experts in various medical specialty fields. The information is typically searchable by topic or keyword and produces materials in response to the HCP's search terms.

These clinical reference resources often contain information about unapproved uses of medical products. Therefore, when sharing SIUU communications in the form of CPGs, reference texts, or materials from independent clinical practice resources, FDA recommends that firms follow the recommendations in Q1, Q2, and Q3, subject to the following additions and modifications.

When a firm shares an SIUU communication in the form of one or more individual section(s) of any of these clinical reference resources, the SIUU communication should include all information from the clinical reference resource necessary for HCPs to interpret the strengths and weaknesses and validity and utility of the information. This may involve the sharing of multiple sections of the clinical reference resource that contain related or linked information. When a firm shares individual section(s) from these clinical reference resources, those individual section(s) should be unaltered/unabridged and extracted directly from the clinical reference resource.

Because unabridged CPGs and reference texts in their entirety generally discuss a wide range of topics and medical products, FDA notes the following exceptions to the recommendations in Q2. When a firm shares an SIUU communication in the form of an unabridged CPG or reference text in its entirety that discusses a wide range of medical products and that discussion is not primarily focused on one or more of a firm's medical products, FDA does not expect a firm to include any of the following:

- A statement disclosing the FDA-approved use(s), including any limitations of use specified in the FDA-required labeling, for each of the firm's medical products mentioned in the CPG or reference text

- A statement disclosing any limitations, restrictions, cautions, or warnings described in the FDA-required labeling about the unapproved use(s) for each of the firm's medical products mentioned in the CPG or reference text

- A copy of or mechanism to obtain the FDA-required labeling for each of the firm's medical products mentioned in the CPG or reference text

- A statement describing the contraindications in the FDA-required labeling for each of the firm's medical products mentioned in the CPG or reference text

- A description of the serious, life-threatening, or fatal risks that are in the 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 (including whether a REMS has been established for any of the firm's medical products mentioned in the CPG or reference text and a description of the goal(s) of the REMS)

Instead, FDA recommends that firms include a more general statement in the SIUU communication, such as, "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."

a. Specific Recommendations for CPGs:

CPGs are generally based on a wide range of evidence, with the goal of making treatment recommendations and describing the different levels of evidence that support those recommendations. When firms share SIUU communications in the form of a CPG, FDA recommends that the CPG have all of the following characteristics:

- 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

- The CPG includes ratings of the recommendations to reflect the quality and strength of evidence that supports each recommendation

- The CPG is revised when important new evidence warrants modifications of current recommendations

- The CPG is generally available through independent distribution channels (e.g., internet sources, book retailers, subscriptions, libraries) where CPGs are sold or are accessible

One helpful resource when considering whether a particular CPG is appropriate to serve as the basis for an SIUU communication is the National Academy of Medicine (NAM)[52] standards for CPG "trustworthiness."[53] CPGs that are consistent with the NAM standards would also be in alignment with the standards FDA has articulated. The NAM standards recommend that CPGs

[52] NAM was formerly known as the Institute of Medicine (IOM) and is one of three academies that make up the National Academies of Sciences, Engineering, and Medicine.

[53] Through the Medicare Improvements for Patients and Providers Act of 2008, Congress required the Secretary of Health and Human Services (HHS) to contract with IOM (through the Agency for Healthcare Research and Quality) to undertake a study that focused on "the best methods used in developing clinical practice guidelines in order to ensure that organizations developing such guidelines have information on approaches that are objective, scientifically valid, and consistent" (Public Law No. 110-275, 122 Stat. 2595). Also, in this legislation, Congress required IOM to submit a report to the Secretary of HHS and the appropriate committees of Congress containing the results of the study, together with recommendations for such legislation and administrative action as IOM determines appropriate. The standards for CPG "trustworthiness," as referred to in this guidance, are taken directly from IOM's study results (as articulated in its report, Robin Graham, et al. eds., Institute of Medicine of the National Academies, Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, *Clinical Practice Guidelines We Can Trust* (2011)), available at https://nap.nationalacademies.org/catalog/13058/clinical-practice-guidelines-we-can-trust.

(1) be based on a systematic review[54] of the existing evidence; (2) be developed by a knowledgeable, multidisciplinary panel of experts and representatives from key affected groups; (3) consider important patient subgroups and patient preferences, as appropriate; (4) be based on an explicit and transparent process by which the CPG is developed and funded that minimizes distortions,[55] biases, and conflicts of interest; (5) provide a clear explanation of the logical relationships between alternative care options and health outcomes, provide clearly articulated recommendations in standardized form, and provide ratings of both quality of evidence and the strength of recommendations; and (6) be reconsidered and revised when important new evidence warrants modifications of recommendations.

Numerous professional organizations develop and disseminate CPGs that are pertinent to their members' clinical practices. In an era of rapidly increasing amounts of scientific information about medical products, CPGs can be a tool to manage this information. However, in light of the proliferation of professional organizations promulgating CPGs and the variations in scope and evidence used for CPG recommendations by these organizations, it is important that firms assess CPGs in a medical practice area to ensure they are consistent with the recommendations in this guidance, including that CPG recommendations have ratings to reflect the strength and quality of evidence supporting those CPG recommendations and that any CPG recommendations are updated when new evidence warrants modification.

b. Specific Recommendations for Reference Texts and Independent Clinical Practice Resources:

When firms share SIUU communications in the form of a reference text or material from independent clinical practice resources, FDA recommends that the reference text or material from an independent clinical practice resource have all of the following characteristics:

- It is published by an independent publisher that is in the business of publishing scientific or medical educational content[56]

- 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

[54] The NAM has defined a systematic review as "a scientific investigation that focuses on a specific question and uses explicit, prespecified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies." Institute of Medicine, *Finding What Works in Health Care: Standards for Systematic Reviews* (Jill Eden et al. eds., The National Academies Press 2011), available at https://nap.nationalacademies.org/catalog/13059/finding-what-works-in-health-care-standards-for-systematic-reviews.

[55] Per NAM, distortion may result from, for example, reliance on incomplete data.

[56] It would be consistent with this recommendation for a firm to fund the production of copies of a reference text or material from an independent clinical practice resource that is already generally available and to provide those copies to HCPs.

- It is authored, edited, and contributed to by experts who have demonstrated expertise in the subject area(s) through education or experience

- It is generally available or sold through independent distribution channels[57] (e.g., internet sources, book retailers, subscriptions, libraries) for medical and scientific educational content

3. Specific Recommendations for Firm-Generated Presentations of Scientific Information from an Accompanying Reprint

In addition to sharing reprints, some firms develop firm-generated presentations of scientific information from an accompanying reprint. Consistent with the above recommendations in this guidance, an SIUU communication in the form of a firm-generated presentation of scientific information from an accompanying reprint should be truthful, non-misleading, factual, and unbiased and provide all information necessary for HCPs to interpret the strengths and weaknesses and validity and utility of the presented information, as further explained in this section.

First, the full reprint(s) should accompany the firm-generated presentation and should be consistent with the recommendations in item 1 in Q4. However, firms 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 made in the firm-generated presentation should be included with those representations within the firm-generated presentation, notwithstanding the recommendations in Q2. For example, if a firm-generated presentation includes information about study results, the firm-generated presentation should include all material aspects of and limitations related to the study design, methodology, and results necessary to interpret the presented information directly with the presented information.

Second, firm-generated presentations should include the disclosures recommended in Q2 of this guidance[58] and should also clearly disclose what portions of the communication are firm-generated. For example, a firm-generated presentation could include the following statement: "This presentation was developed by FIRM X."

Third, firm-generated presentations should be consistent with the recommendations in this guidance regarding presentational considerations (see Q3).

[57] FDA recognizes that individual chapters of reference texts may not be generally available through these channels; this language is referring to general availability of the complete reference text.

[58] To the extent that recommended disclosures apply to both the firm-generated presentation and the reprint, FDA does not generally expect that firms repeat the recommended disclosures in both the firm-generated presentation and separately in an attachment to the reprint(s). However, firms should ensure that all recommended disclosures that are material to specific representations made in the firm-generated presentation are at a minimum included with such representations in the firm-generated presentation.

Fourth, to ensure that an SIUU communication in the form of a firm-generated presentation of scientific information from an accompanying reprint is truthful, non-misleading, factual, and unbiased, the firm-generated presentation should not, for example, do any of the following:

- 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 (e.g., excerpts, quotes, paraphrases, conclusions) 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 conclusions or representations about safety or effectiveness for the unapproved use, even if an accurate reflection of the statements in the reprint, without attributing that statement expressly to the reprint and without immediately following it with the statement identifying any authors, editors, or other contributors to the reprint(s) who were employees of or consultants to or who received compensation from the firm at the time of writing, editing, or contributing to the reprint

- 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