Talk This Way: FDA Provides Guidelines on Medical Product Communications Consistent With the FDA-Required Labeling

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Channeling Aerosmith's 1975 single, "Walk This Way," and the song lyric "Talk This Way," the Food and Drug Administration issued a draft guidance to industry on how it can communicate certain types of product information consistent with, but not actually provided in, the product labeling.[1] The draft, "Medical Product Communications That Are Consistent With the FDA-Required Labeling – Questions and Answers," which applies to drugs and medical devices, is one of a number of agency releases issued recently about product communications.[2] FDA continues to evaluate how to handle product information dissemination, particularly after it has lost court cases relating to off-label promotion (about which we have written).[3] While FDA's recent guidances and other written communications are not legally binding, they offer insight into the agency's current thinking.

This Bulletin highlights key elements of the draft guidance and offers our observations. FDA has requested that any comments on this draft guidance be submitted within 60 days of the Federal Register notice, dated January 19, 2017, announcing the document's availability.

Highlights of the Draft Guidance

The draft guidance provides recommendations on communicating information, primarily in a Question-and-Answer format, that is consistent with the required labeling, but not contained in the FDA-approved or cleared labeling. The guidance applies to drugs and medical devices, which are referred to as "medical products" throughout the guidance. To be consistent with the required labeling, communications must satisfy three factors.

- **Factor 1:** How the information in the communication compares to the information about the conditions of use in the required labeling, focusing on the following areas to evaluate whether they are different from the FDA-required labeling: (1) indication, (2) patient population, (3) limitations and directions for handling/use, and (4) dosing/administration.

- **Factor 2:** Whether the representations or suggestions increase the potential for harm to health when compared to the FDA-required labeling.

1 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537130.pdf

2 FDA also recently issued a final rule on tobacco products that includes revisions to the regulatory definition of "intended uses" for both drugs and medical devices. FDA has added a sentence to the definitions stating that a manufacturer's intended use will be determined on a "totality of the evidence" standard. If the totality of the evidence shows that the manufacturer objectively intends that its drug or device be introduced into interstate commerce for a use other than its approved or cleared use, the manufacturer needs to provide adequate labeling for that use. The changes are intended to clarify, rather than change, FDA's current practice regarding evidence of intended uses and will apply to drugs and devices generally, not only tobacco-derived products (https://www.gpo.gov/fdsys/pkg/FR-2017-01-09/pdf/2016-31950.pdf). Separately, FDA released a memorandum on public health issues and First Amendment considerations for off-label communications (https://www.federalregister.gov/documents/2017/01/19/2017-01013/manufacturer-communications-regarding-unapproved-uses-of-approved-or-cleared-medical-products), and another draft guidance, "Communications With Payors, Formulary Committees, and Similar Entities" (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537347.pdf). AGG is preparing separate Bulletins on those documents.

3 See http://www.agg.com/Fight-the-Good-Fight-Every-Moment-Do-Recent-First-Amendment-Court-Developments-Deal-a-Blow-to-the-Government-03-17-2016/; http://www.agg.com/its-deja-vu-all-over-again--fda-sued-again-in-off-label-promotion-case-09-21-2015/.

- e.g., a drug is reserved for third-line use because of safety issues; if communications about the drug state or imply that all patients should try the product (without determining if first or second-line therapies are suitable), the communication would not be consistent with the safety profile approved by FDA

- **Factor 3:** Whether the directions for use in the FDA-required labeling allow the product to be safety and effectively used as described in the communication; if not, the communication is not consistent.

Communication that includes consistent information not found in the required label does not, alone, provide evidence of a new intended use; however, the guidance focuses on the substantiation required to ensure that the communication is not false or misleading.

- representations or suggestions must be grounded in science and presented with appropriate context
- communication should include the limitations of the evidence
- but, if the communication relies on an inadequate study, even including those limitations, the communication may be considered misleading

FDA provides examples of communications that could be consistent with the required labeling:

- information describing a head-to-head study between one product and another product with the same approved indication
- information that provides further context or information on adverse reactions
- information about the onset of action for a product
- information on the long-term safety of a product approved for chronic use
- information about the product's effects on a specific subgroup within the approved patient population
- patient-reported outcomes when the product is used for its FDA-approved or cleared indication in the appropriate population
- information on product convenience
- additional information on the product's mechanism of action

While some of these examples may seem to provide flexibility in communications (e.g., including patient-reported outcomes or product convenience information), FDA also provides examples of information not consistent with the required labeling.

- information on using the product to treat or diagnose a condition other than the one described in the label
- information about using the product to treat a patient outside the appropriate population
- information on using the product to treat a different stage or severity than the one approved
- information about the product as a monotherapy when it is only approved for use with other products
- information about using the product through a different route of administration
- information about using the product in another strength or dosing regimen than the one approved or cleared
- information about using the product in a different dosage form

FDA provides general recommendations for presenting information in a truthful and non-misleading manner (we offer some of FDA's representative examples below):

- accurately represent study results and other data or information used to support the communication, and clearly disclose the material aspects and limitations of the study design, methodology, and results
- accurately characterize the relevant information about the product, including unfavorable or inconsistent findings

    - if a firm is presenting efficacy results from a study that had two endpoints, and the product failed to demonstrate an effect on one of those endpoints, the company should disclose this rather than presenting only the positive efficacy results

- if the communication includes information not found in the label, but related to information in the label, that related information should be noted
    - e.g., if a communication lists the adverse events that have actually occurred, it should also provide the adverse events from the required labeling

FDA provides two examples of appropriate, label-consistent communications:

- a drug product is indicated for use in both males and females to treat a condition, and the pivotal study of the product provides the supporting data with no limitations or special considerations relating to gender
    - the manufacturer may develop materials that note this lack of limitations, as the communication would not be expected to increase potential harm to patients, and the product could be used safely and effectively to treat the condition, regardless of gender, by following the directions in the FDA-required labeling
- an implantable device is approved as an adjunctive therapy
    - the directions for use do not prescribe a specific use schedule and, in the clinical study supporting the device's premarket approval application, approximately half of the patients using the device reported severe headaches
    - the company enrolls patients in a post-marketing registry, and the patients have follow-up clinical visits and use a diary to record symptoms and adverse events
    - data suggests that patients using the device more frequently and for a shorter period of time, which is consistent with the approved labeling, have a reduced incidence of headaches compared to that reported in the approved labeling
    - the manufacturer may develop communications including this information if the materials fully explain the registry (patient numbers, patient population, outcome measures, device use, and the adverse events/symptoms reported by patients), along with qualifying the limitations of the information (no conclusions can be drawn about the relationship between the use patterns and the incidence of symptoms)
    - the communications must also disclose the data from the premarket clinical study

In contrast, the guidance describes an improper drug communication:

- Drug A and Drug B are approved for the same indication and have a comparable risk profile
- the manufacturer of Drug A evaluates the safety and efficacy of Drug A versus placebo in a randomized, double-blind study, and does the same for Drug B
- however, the study is not designed to test the non-inferiority or superiority of Drug A against Drug B
- if the company develops promotional materials about Drug A's superiority to Drug B for the indication, that information would be consistent with the label, but it would be misleading
- FDA could still take enforcement action against the company for making claims that mislead by failing to describe the limitations of the study and which are not supported by appropriate evidence

AGG Observations

- FDA continues to struggle with how to address off-label communications, but it appears willing to allow distribution of certain information that, while not actually in the approved labeling, may be consistent with the labeling.
- The "truthful, not misleading" concept, which is evolving from lawsuits and trade association recommendations (although it is not the "law of the land"), is a running theme in the draft.
- Notwithstanding FDA's apparent willingness to be more open-minded on the subject, it reiterates that accurate information can still be misleading.

- e.g., the agency notes that patient-reported outcomes and information about product convenience may be appropriate in some contexts
- but, without appropriate qualifiers, this information can be misleading
- companies should be careful to prominently identify the limitations of any patient-reported outcomes, and these outcomes should not replace the safety information in the FDA-approved label

- We repeat our cautionary warning to clients that something may be truthful in isolation, but misleading in context.
- FDA will continue to evaluate whether claims are substantiated.

    - communications should note the limitations of studies, but a study may be so inadequate to support the claims being made that a company should not structure promotional messaging around the study, because FDA has clarified that even disclosing the study's limitations is not sufficient to correct the overall misleading message

- We note that, pending updates to FDA's policy on off-label communications, recent enforcement efforts continue to focus on communications that are misleading.
- Transparency and full disclosure, whereby the reader of the information is properly educated as to the good, bad, and ugly, is consistent with the concept of providing truthful, not misleading information.
- Companies' promotional review committees must continue to evaluate medical product communications that, while consistent with the FDA-required labeling, are provided in a manner that can withstand an FDA challenge (or scrutiny from a competitor, plaintiff's lawyer, state agency, or the Department of Justice, for example).
- "Talk This Way" is only useful if you "Walk This Way," such that the materials provided are consistent with FDA and company standards to ensure accurate and balanced information.

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