ROPES & GRAY ALERT

FDA Regulatory ▪ Government Enforcement / White Collar Crime

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FDA Issues Three Key Documents Relating to Medical Product Manufacturer Communications

On January 18, 2017, the Food and Drug Administration ("FDA") released three key documents outlining the agency's current thinking regarding drug and device manufacturers' communication of information not contained in FDA-approved labeling. FDA issued two draft guidance documents laying out FDA's position with respect to (1) manufacturer communications with payors, formulary committees, and similar entities, and (2) manufacturer communications consistent with FDA-required labeling. The payor guidance document was issued in response to a request from the Medical Information Working Group ("MIWG"), an *ad hoc* coalition of drug and device manufacturers co-represented by Ropes & Gray. Additionally, in response to comments received during a two-day public hearing held on November 9-10, 2016, FDA published a memorandum outlining the agency's current thinking with respect to the First Amendment implications of FDA's regulation of manufacturer communications about unapproved uses of approved or cleared medical products.

These documents represent a final attempt by the outgoing Administration to impact the agency's regulatory approach going forward. While it is possible that the new Administration will have different views on some or all of the positions FDA has set forth, particularly in the First Amendment memorandum, these documents represent long-awaited commentary on issues of critical importance to industry.

Draft Guidance on Payor Communications

The draft guidance document, entitled "Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities—Questions and Answers," addresses two types of manufacturer communications with payors. First, it addresses communication of healthcare economic information ("HCEI") about drug products to payors pursuant to Section 114 of the Food and Drug Modernization Act of 1997 ("FDAMA 114"), as amended by the 21st Century Cures Act. Second, and most significantly, it creates a new safe harbor for communications with payors about investigational drugs and devices.

1. Communication of HCEI Under FDAMA 114

Guidance on drug manufacturer communication of HCEI to payors has been long awaited by industry, which has sought clarification of FDAMA 114 since the statute was initially enacted in 1997. Under FDAMA 114, drug product manufacturers are permitted to communicate HCEI with certain audiences if such information is related to an approved indication and is supported by competent and reliable scientific evidence ("CARSE"). The draft guidance defines and clarifies key elements to qualify for the FDAMA 114 safe harbor, including (1) what information qualifies as HCEI; (2) the appropriate audience for the information; (3) when information "relates to an approved indication"; (4) the required level of evidentiary support; and (5) the disclosures that should accompany communications.

- What Information Qualifies as HCEI? Under FDAMA 114, as amended by the 21st Century Cures Act, HCEI is defined as "any analysis (including the clinical data, inputs, clinical or other assumptions, methods, results, and other components underlying or comprising the analysis) that identifies, measures, or describes the economic consequences, which may be based on the separate or aggregated clinical consequences of the represented health outcomes, of the use of a drug." FDA's draft guidance clarifies that HCEI may include

comparative analyses and may be presented in a variety of different formats (e.g., evidence dossier, reprint, or software model).

- Who is the Appropriate Audience? Under FDAMA 114, as amended, HCEI may be communicated to "a payor, formulary committee, or other similar entity with knowledge and expertise in the area of health care economic analysis, carrying out its responsibilities for the selection of drugs for coverage or reimbursement[.]" In determining whether a particular audience qualifies under FDAMA 114, FDA's draft guidance clarifies that the agency will consider whether the entity (1) is constituted to consider HCEI and other information through a deliberative process, (2) has the appropriate range of knowledge to interpret HCEI, and (3) makes population-based decisions (as contrasted with the individual treatment decisions made by prescribers).

- When Does Information "Relate to an Approved Indication"? Under FDAMA 114, as amended, HCEI must "relate to an [approved] indication." FDA's draft guidance clarifies that HCEI relates to an approved indication if it "relate[s] to the disease or condition, manifestation of the disease or condition, or symptoms associated with the disease or condition in the patient population for which the drug is indicated in the FDA-approved labeling." The draft guidance provides examples of such HCEI, including but not limited to data on long-term use, dosing regimens that vary from approved labeling, patient subgroups, and clinical outcome assessments.

- What is the Required Level of Evidentiary Support? FDA's draft guidance interprets CARSE as meaning that HCEI should be "developed using generally-accepted scientific standards, appropriate for the information being conveyed, that yield accurate and reliable results." FDA indicates that it would look to research practices of authoritative bodies, such as the International Society for Pharmacoeconomic and Outcomes Research ("ISPOR") and the Patient-Centered Outcomes Research Institute ("PCORI"), for guidance on generally accepted scientific standards for HCEI. The draft guidance also clarifies that FDA intends to apply the CARSE standard to all components of HCEI, including inputs and assumptions related to both economic consequences and clinical outcomes.

- What Disclosures Should Accompany HCEI? The draft guidance provides an extensive list of information that should be included when disseminating HCEI, including information on study design and methodology, generalizability, limitations, sensitivity analysis, and other material information. While many of these disclosures appear reasonable, others may be challenging from a practical standpoint or arguably go beyond the statutory requirement to include "a statement describing any material differences between the health care economic information and the [approved] labeling."

2. Communications Related to Investigational Products

In addition to clarifying the FDAMA 114 safe harbor, the draft guidance would create a new safe harbor for communications with payors about investigational products. Industry has previously called on FDA to clarify its policy in this area, given the critical importance of payors having access to information on pipeline products prior to approval or clearance to minimize coverage delays for patients.

The new safe harbor for communications about investigational products by definition would apply only to "drugs and devices that are not yet approved/cleared by FDA for any use (but which must be approved/cleared to be legally marketed)." It would not apply to communications related to investigational uses of approved or cleared products, which would presumably be limited to communication under other safe harbors (e.g., scientific exchange, responses to unsolicited requests, and dissemination of reprints).

In detailing the contours of the safe harbor, the draft guidance provides that FDA does not intend to object to communication of certain types of information about investigational products to payors, including but not limited to

product information, factual presentations from clinical or preclinical studies, anticipated timeline for FDA approval/clearance, and product pricing information.

When communicating pre-approval information to payors, the draft guidance recommends that manufacturers include (1) a clear statement that the product is under investigation and that the safety or effectiveness of the product has not been established, and (2) information on the stage on product development. The draft guidance also suggests that manufacturers update payors if previously communicated information becomes outdated as a result of significant changes or new information about the investigational product (e.g., failure to meet primary efficacy endpoint in a phase 3 study).

Draft Guidance on Communications Consistent with FDA-Required Labeling

The second draft guidance document, entitled "Medical Product Communications That Are Consistent With the FDA-Required Labeling—Questions and Answers," addresses circumstances in which manufacturers may communicate information that is not contained in the required product labeling, but which is consistent with such labeling. The draft guidance explains that communication of information not contained in, but consistent with, FDA-required labeling will not alone be considered evidence of a new intended use. The draft guidance also affirms that FDA will not consider such information false or misleading merely because it is not supported by studies meeting the applicable approval standard for the product—i.e., for prescription drugs, the substantial evidence standard.

The draft guidance defines FDA-required labeling to mean the labeling reviewed and approved by FDA in a marketing application for a medical product (e.g., new drug application or a premarket approval application for a medical device). For products that do not require premarket approval, such as medical devices subject to premarket notification ("510(k)" clearance) or that are exempt from premarket notification, FDA states that required labeling includes the labeling relied on to provide adequate directions for use and other information required to appear in labeling.

The draft guidance outlines three factors for determining whether a communication is consistent with the FDA-required labeling and therefore will not be considered violative.

- Conditions of Use. FDA states that the information in the communication relating to the product's conditions of use should be consistent with the FDA-required labeling for the product. FDA states that it would not consider a communication to be consistent with the required labeling if, for example, the communication represents the product for a different indication or patient population than reflected in the required labeling, or suggests conflicting information on limitations or directions for using the product, or its route of administration or strength.

- Potential to Increase Risk of Harm. The draft guidance states that, if a communication alters the benefit-risk profile of a product in a way that may result in increased harm to health, this indicates that the communication is not consistent with the FDA-required labeling.

- Ability to Use the Product Safely Under Required Labeling. The draft guidance states that, unless the directions for use in the FDA-required labeling enable the product to be used safely and effectively for the conditions suggested in the communication, the communication is not consistent with the FDA-required labeling.

FDA also provides examples of information that would and would not be considered consistent with the required labeling. Information consistent with the required labeling may include, for example, comparative information based on "a" head-to-head study with another medical product approved/cleared for the same indication (raising the question of whether FDA is abandoning the standard of *two* head-to-head studies for drug comparative claims), information on long-term safety or efficacy of products approved/cleared for chronic use, information on effects in a patient subgroup included within the approved/cleared patient population, or additional context on the product's

mechanism of action described in the FDA-required labeling. Examples of information that would not be consistent with the FDA-required labeling include information on a different disease or condition, patients outside the approved/cleared patient population, a different disease stage or severity, or dosages or dosage forms that differ from the FDA-required labeling.

In addition to addressing consistency with FDA-approved labeling, the draft guidance outlines criteria for evaluating whether a communication may be considered false or misleading. FDA states that any data, studies, or analyses relied on should be "scientifically appropriate and statistically sound to support the representations or suggestions made in the communication." In addition, FDA states that the information must be presented in a truthful and non-misleading manner, with appropriate disclosures and contextual information.

Although FDA's drug regulations have long permitted manufacturers to disseminate some promotional information "consistent with" but not the same as the FDA-required labeling, the draft guidance represents the first time FDA has provided detailed guidance on how it assesses consistency with the approved labeling. The draft guidance also addresses medical devices in addition to drugs, which may be helpful to device manufacturers given the relative lack of device-specific rules or guidance in this area.

First Amendment Memorandum

As discussed in a previous Ropes & Gray Alert, FDA held a two-day public hearing relating to FDA's regulation of off-label communications on November 9-10, 2016. Ropes & Gray partner Kellie Combs (Washington, D.C.) testified at the hearing on behalf of MIWG, expressing concern that FDA had "fail[ed] to address or even mention First and Fifth Amendment dictates." FDA recently acknowledged the concern that it "had not sufficiently discussed the First Amendment in the notice of the public hearing," and published a memorandum entitled "Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products."

The memorandum reaffirms and seeks to bolster the basis for FDA's long-standing restrictions on manufacturer speech regarding unapproved uses of medical products. It focuses on explaining the public health interests served by the agency's current regulatory approach, describes harms associated with false or misleading off-label promotion, and asserts that various alternative approaches that have been proposed would be inadequate. In response, industry is likely to argue that the memorandum downplays the public health benefits of off-label use, instead stressing isolated historical examples of harm from unapproved uses, and inadequately considers the impact of recent court decisions challenging FDA's regulatory framework on First Amendment grounds, including *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012) and *Amarin Pharma v. FDA*, 119 F. Supp. 3d 196 (S.D.N.Y. 2015). It remains to be seen whether, under the new Administration, FDA will continue to advance the arguments set forth in the memorandum.

FDA will accept comments to the two draft guidance documents and First Amendment memorandum until April 19, 2017. If you would like to discuss the foregoing or any other related matter, please contact any member of Ropes & Gray's FDA regulatory or government enforcement practices or your usual Ropes & Gray advisor.