

Health Industry Alert

January 27, 2017

FDA Offers Some Clarity (But Few Concessions) on Off-Label Communication of Medical Products

Among the flurry of policies the Food and Drug Administration (FDA) released in the waning days of the Obama administration are several documents that seek to clarify the agency's positions on communications about medical products.

The documents are:

- Draft Guidance: Medical Product Communications That Are Consistent with the FDA-Required Labeling¹ (released January 18, 2017; available here)
- Draft Guidance: Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities² (released January 18, 2017; available here)
- Memorandum, Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products³ (released January 19, 2017; available here)
- Final Rule, Clarification of When Products Made or Derived from Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses"⁴ (published January 9, 2017, available here).

These documents follow recent case law that has eroded FDA's authority to prohibit truthful and nonmisleading "off-label" communications, and ongoing requests from industry for greater guidance on the scope of permissible communications. Taken together, FDA appears intent on preserving its enforcement authority over off-label promotion.

¹ FDA, Draft Guidance, Medical Product Communications That Are Consistent with the FDA-Required Labeling – Questions and Answers (Jan. 18, 2017), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537130.pdf> (hereinafter "Consistent Communications Draft Guidance").

² FDA, Draft Guidance, Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities – Questions and Answers (Jan. 18, 2017), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537347.pdf> (hereinafter "Payor Communications Draft Guidance").

³ Memorandum, Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products (Jan. 19, 2017), available at <https://www.regulations.gov/document?D=FDA-2016-N-1149-0040> (hereinafter "Memorandum").

⁴ Final Rule, Clarification of When Products Made or Derived from Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses," 82 Fed. Reg. 2,193 (Jan. 9, 2017), available at <https://www.gpo.gov/fdsys/pkg/FR-2017-01-09/pdf/2016-31950.pdf> (hereinafter "Final Rule").

With its pair of draft guidance documents, FDA slightly broadens the scope of permissible communications related to approved or cleared medical products, and the sharing of health care economic information (HCEI) relating to approved or cleared medical products and unapproved medical products, such as investigational new drugs and devices.

At the same time, FDA firmly defends its authority to prohibit off-label promotion under First Amendment jurisprudence (in the memorandum and in the preamble to the final rule).

These documents are described in greater detail below.

Consistent Communications Draft Guidance

Through a series of questions and answers, the Draft Guidance describes FDA's current thinking regarding dissemination of information not appearing on FDA-required labeling, which includes the FDA-reviewed labeling on approved products and adequate directions for use and other information appearing on the labels of cleared devices. As applied to devices, this Draft Guidance applies to labeling required for products for which FDA permits marketing through premarket approval, 510(k), de novo classification or Humanitarian Device Exemption pathways, and to devices that are exempt from premarket notification.⁵ The Draft Guidance applies to human and animal drugs, biologics and medical devices. The Draft Guidance does not address considerations relating to the approval of generic drugs and biosimilars in determining whether proposed labeling has been previously approved for the reference product, and it presumably does not apply to lawfully compounded drugs. Specifically, the Draft Guidance describes the types of off-label information that manufacturers may and may not convey in compliance with the legal requirement that such information be truthful and not misleading. FDA explains that providing information outside the FDA-required labeling will not, alone, be considered evidence of a new intended use (in violation of the Food, Drug, and Cosmetic Act (FDCA) § 502(f)), so long as the information is "consistent" with the FDA-required labeling.⁶ The Draft Guidance outlines the factors FDA will use to determine whether information is consistent for purposes of this analysis. Under the Draft Guidance, a communication is only "consistent" with the FDA-required labeling if it meets all of the following factors:⁷

- **Comparison to conditions of use in the required labeling:** Representations must not relate to a different indication; patient population; directions for handling/preparing/use; or recommended dosage, strength or route of administration from the required labeling.
- **Potential to harm health:** Representations must not alter the risk-benefit profile in any way that could result in increased harm to health.

⁵ Consistent Communications Draft Guidance, at 1 n.4.

⁶ *Id.* at 3.

⁷ *Id.* at 3–5.

- Comparison to directions for use: The directions for use must enable the product to be used safely and effectively under the conditions described in the representation.

Following these vague and somewhat overlapping factors, FDA provides examples of communications that pass the test of consistency, including information

- based on a comparison of the safety or efficacy of a medical product for its approved/cleared indication to another medical product approved/cleared for the same indication
- that provides additional context about the adverse reactions associated with an approved/cleared medical product
- about the onset of action of the product for its approved/cleared indication and dosing/use regimen
- about the long-term safety and/or efficacy of products that are approved/cleared for chronic use (e.g., a firm could share data showing persistent safety and efficacy over an 18-month period for a product approved/cleared based on a 24-week study)
- about the effects or use of a product in specific patient subgroups that are included in its approved/cleared patient population
- concerning the effects of a product that comes directly from the patient (i.e., patient-reported outcomes) when the product is used for its FDA-approved/cleared indication and patient population
- concerning product convenience
- that provides additional context about the mechanism of action described in the FDA-required labeling.⁸

Some of these examples appear to signal a slight thawing in FDA's approach to communications made related to drugs, particularly with respect to information about longer-term safety and efficacy, specific patient subgroups, patient-reported outcomes and mechanism of action.

The agency also offers examples of communications that would run afoul of these factors. FDA would not consider information about the use of a product to treat a different disease or condition; a different patient population; or a different stage, severity or manifestation of a disease to be consistent with required labeling. The same goes for information that differs from the required labeling about the strength, dosage or regimen, route of administration or use as a monotherapy (versus adjunct use).

In addition, these Q&As set forth FDA's expectations regarding the appropriate context of scientific data used to communicate information that exceeds the scope of the required labeling. For the information to be considered truthful and not misleading, manufacturers should communicate only "scientifically appropriate and statistically sound" information and should disclose material limitations of referenced studies, including those relating to strength, power, and generalizability. The bar for demonstrating

⁸ Consistent Communications Draft Guidance, at 6–7

“scientifically appropriate and statistically sound” information is seemingly lower than that for FDA’s “substantial evidence” standard.⁹ FDA will not consider communications that otherwise qualify as “consistent” to be false or misleading solely because the firm cannot offer evidence that would meet the applicable approval/clearance standard.¹⁰ The agency reasons that the product would have already met the safety and effectiveness standard for approval/clearance—and these communications would be “consistent” with that approval/clearance. However, FDA still reserves the right to find such a communication to be false or misleading for other reasons. The Draft Guidance also notes that off-label communications must comport with other provisions of the FDCA, Public Health Service Act and other applicable regulations.

Comments must be submitted by April 19, 2017.

Payor Communications Draft Guidance

This Draft Guidance describes FDA’s current thinking regarding medical product manufacturers’ communication of HCEI to payors (e.g., health insurance companies); formulary committees (e.g., pharmacy and therapeutics committees); drug information centers; technology assessment bodies, and other entities that make drug selection, coverage and reimbursement decisions on a population basis. Communications to individual health care providers/prescribers and consumers are not contemplated under the Draft Guidance.¹¹

FDA does not limit the methods for communicating competent and reliable scientific evidence (CARSE), which could be conveyed in an evidence dossier, journal reprint, software, budget model or another form.¹² The CARSE standard applies to all HCEI, including inputs and assumptions relating to both clinical outcomes and economic consequences.¹³ To ensure that it is not misleading, HCEI should be developed using generally accepted scientific standards. Specifically, communications to payor entities should include clear information about study design and methodology, such as the type of analysis, modeling, patient population, perspective, treatment comparator, time horizon, cost estimates and assumptions; any factors that limit its generalizability; limitations that affect interpretability or reliability of the analysis; sensitivity analysis; and additional information to ensure balance, including sharing the FDA-approved labeling itself and prominent statements describing material differences from approved labeling, disclosure of any omitted studies or data sources, risk information related to clinical assumptions, and disclosure of any potential financial or affiliation biases.¹⁴

The FDCA, which was amended by Section 3037 of the 21st Century Cures Act (Public Law 114-255), requires that HCEI relate to an approved indication, and the Draft Guidance provides examples of

⁹ *Id.* at 7; see U.S.C. §§ 355(d); 21 C.F.R. § 202.1(e)(6)–(7).

¹⁰ Consistent Communications Draft Guidance, at 9.

¹¹ Communications with Payors Draft Guidance, at 4–5.

¹² *Id.*

¹³ *Id.* at 9.

¹⁴ *Id.* at 9–12.

information that would—and would not—satisfy this requirement. FDA considers HCEI to relate to an approved indication if it is consistent with the approved duration of treatment and approved dosage forms and strengths. However, HCEI may relate to effects within study subgroups not included on the labeling, effects in practice settings other than those studied and effects on validated surrogate endpoints, as well as impact on hospital stays, clinical outcomes assessments (COAs) and overall burden of illness.¹⁵ FDA reminds firms that HCEI disseminated in accordance with the statutory allowance for HCEI (in Section 502(a) of the FDCA) constitutes promotion and is thus subject to requirements for submission of promotional materials, including the postmarketing requirement to submit such materials to FDA at the time of initial dissemination.¹⁶ Responding to unsolicited requests from payor entities regarding off-label uses of approved products is not addressed in this Draft Guidance, but is the subject of prior guidance.

This Draft Guidance also addresses the communication of HCEI relating to unapproved medical products, such as investigational drugs and devices. Because payor entities must plan for, and make, coverage and payment decisions in advance, FDA will not object to manufacturers sharing certain truthful and nonmisleading HCEI regarding unapproved, investigational products. When it comports with the aforementioned CARSE standards for complete and balanced scientific information, firms may share product information (e.g., drug class, device design); indication and patient population being studied; objective results of clinical/preclinical studies; anticipated timeline of FDA review; and product pricing information and related programs (e.g., patient assistance programs).¹⁷ In addition, such communications should include a clear statement that the product is under investigation, as well as the stage of product development (e.g., clinical trial phase); should not make any representations regarding safety or effectiveness; and may be made to only appropriate HCEI audiences, not to individual providers. Finally, the agency suggests that firms update previously shared HCEI once it becomes outdated.¹⁸

Comments must be submitted by April 19, 2017.

Memorandum on Communications and the First Amendment

On January 18, 2017, FDA released a memorandum, Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products reasserting its position that regulation of off-label promotion is permissible under the First Amendment, even in light of recent jurisprudence limiting its authority. FDA held a two-day public hearing in November 2016 to address its authority to regulate communications regarding unapproved uses of approved or cleared medical products, and solicited comment on the issue. In an apparent response to comments that FDA did not sufficiently discuss the First Amendment in the notice for the public hearing, FDA reopened the comment period to publish this Memorandum.¹⁹ The agency

¹⁵ *Id.* at 6–8.

¹⁶ *Id.* at 14–15 (referencing the standards codified at 21 CF.R. § 314.81(b)(3)(i), *inter alia*).

¹⁷ Communications with Payors Draft Guidance, at 16.

¹⁸ *Id.* at 16–17.

¹⁹ Memorandum, at 1.

seeks public comment on how best to reconcile the interests of public health and safety with First Amendment jurisprudence.

FDA dedicates a considerable portion of the 60-page Memorandum to establishing the legal background and discussing the competing public health interests at stake. FDA identifies seven public health interests advanced by its policies, including preventing public harm, motivating the development of robust scientific data, limiting diversion of health care resources toward ineffective treatments, protecting the integrity and reliability of promotional information, and maintaining incentives for clinical trial participation. The Memorandum lists only two public health interests supported by allowing broad discussion of unapproved uses for approved products: supporting informed decisionmaking for patient treatment and furthering scientific research.²⁰

FDA also defends its legal authority to use communications made by firms as evidence of a product's intended use, despite the recent series of federal court cases that have signaled increased latitude for firms to promote off-label uses on the basis that such statements are considered a protected form of speech. FDA seeks to narrow the holding in *United States v. Caronia*, in which the 2nd Circuit found that FDA could not prohibit truthful and nonmisleading speech promoting an off-label use of an FDA-approved drug.²¹ *Caronia* set the stage for *Amarin Pharma, Inc. v. United States*, in which a New York district court held that *Caronia* foreclosed reliance on truthful and nonmisleading speech alone as serving as evidence of intended use for purposes of a misbranding action.²² FDA asserts that *Caronia* does not actually limit the agency's enforcement reach because the 2nd Circuit has since written in dicta that "*Caronia* left open the government's ability to prove misbranding on a theory that promotional speech provides evidence that a drug is intended for a use that is not included on the drug's FDA-approved label."²³

The agency also details its contention that it may regulate speech under the framework set forth in *Central Hudson Gas & Electric Corp. v. Public Service Commission*, which lays out a four-part test for determining whether restrictions on commercial speech violate the First Amendment.²⁴ Under *Central Hudson*, if commercial speech is truthful or "potentially misleading" (i.e., not proven to be misleading), the government may still impose restrictions on the speech if the restrictions advance a "substantial" government interest and are no "more extensive than is necessary to serve that interest."²⁵ FDA asserts that the court in *Caronia* did not consider all of the public health interests advanced by FDA's approach, and it notes that the court did not have the benefit of considering a recent Canadian study showing an association between unapproved uses and adverse drug events.²⁶ Because FDA's interest in promoting

²⁰ *Id.* at 17–8.

²¹ 703 F.3d 149, 157 (2d Cir. 2012).

²² *Amarin Pharms., Inc. v. United States*, 119 F. Supp. 3d 196, 235-36 (S.D.N.Y. 2015).

²³ Memorandum, at 22 (quoting *United States ex rel. Polansky v. Pfizer, Inc.*, 822 F.3d 613, 615 n.2 (2d Cir. 2016)).

²⁴ Memorandum, at 23.

²⁵ *Central Hudson Gas & Electric Corp. v. Public Service Comm'n*, 447 U.S. 557, 566 (1980).

²⁶ Memorandum, at 23-4.

public health is “substantial,” the agency contends that it could restrict even truthful and not inherently misleading speech under this framework. Nonetheless, FDA seeks public comment on these restrictions.

After presenting its position on why its current approach is consistent with case law, FDA identifies alternative approaches to addressing off-label promotion. FDA ultimately rejects all of the alternatives because “none of them appear to integrate the complex mix of numerous, and sometimes competing, interests at play and thus do not advance those multiple interests.”²⁷ They include prohibiting altogether the use and/or prescribing of an approved/cleared medical product for an unapproved use, barring approval of generics and other affected products until all periods of exclusivity on the reference product have expired, limiting Medicare and Medicaid reimbursement to approved uses, allowing firms to actively promote an unapproved use as long as they disclose that the use is unapproved and include other appropriate warnings, educating health care providers and patients to differentiate false and misleading promotion from truthful and nonmisleading information, taxing firms more heavily for sales of products for unapproved uses than for approved uses, permitting promotion of unapproved uses listed in medical compendia and limiting evidence that could be considered relevant to intended use to speech that the government can prove is false or misleading.

Although FDA did not find any of these alternatives suitable, the agency purportedly continues to re-examine its position relating to firm communications regarding unapproved uses of approved/cleared medical products and seeks public comment on these proposals.

Comments must be submitted by April 19, 2017.

Final Rule on Definition of “Intended Uses”

On January 9, 2017, FDA published a final rule, Clarification of When Products Made or Derived from Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding “Intended Uses” which amends the definition of “intended use” for purposes of drugs (21 C.F.R. § 201.128) and devices (§ 801.4).²⁸ The actual revisions to the regulatory text do not reflect a change in FDA policy; instead, FDA is updating the regulations to reflect how it currently applies its policies.²⁹ Although the bulk of the Final Rule focuses on products derived from tobacco, FDA makes clear that these changes apply to all drugs and devices. The agency is revising these regulatory definitions to clarify that the agency does not, “absent extraordinary circumstances, . . . regard a firm as intending an unapproved new use for an approved or cleared medical product based solely on that firm’s knowledge that the product was being prescribed or used by doctors for such use.”³⁰ However, FDA will examine all relevant evidence in determining whether a firm has established a new intended use, which may include the firm’s knowledge that health care providers are prescribing or using its approved/cleared

²⁷ *Id.* at 26.

²⁸ 82 *Fed. Reg.* 2,193 (Jan. 9, 2017), available at <https://www.gpo.gov/fdsys/pkg/FR-2017-01-09/pdf/2016-31950.pdf> (referencing 21 C.F.R. §§ 201.128 & 801.4).

²⁹ *Id.* at 2,194.

³⁰ *Id.* at 2,204

medical product for an unapproved use.³¹ In making this clarification, FDA re-emphasizes its position that the agency may look to any relevant source in determining a product's new intended use. FDA also explains in the preamble that sources of evidence are not limited to published marketing materials, but also include internal documents and circumstances surrounding the sale of products.³² In addition, FDA noted that several commenters urged FDA to confirm that truthful and nonmisleading speech cannot form the basis of a firm's intended use of a medical product, based on the holding in *Caronia*. FDA responded that it is in the process of re-examining these policies (and separately released the Memorandum described above a week later). Nevertheless, FDA asserted its legal authority to look to any relevant source of information as evidence of a new intended use, supported by much of the same legal analysis and discussion presented in the Memorandum.

Given the timing and the depth of FDA's legal analysis in both the Memorandum and the preamble of the Final Rule, the agency is making a concerted effort to defend its role in regulating off-label communications and, by extension, the centrality of the premarket review of intended uses of medical products. Meanwhile, FDA does loosen the reins on permissible communications in its two draft guidances, if only very slightly.

These policies, and the extent of their enforcement, could change under new FDA leadership, and the Trump administration has already taken steps to allow for reconsideration of policies issued under the Obama administration. On January 20, 2017, the Trump administration issued a Presidential Memorandum, available here, that instructs heads of executive departments and agencies not to send new rules or guidances to the Office of the Federal Register until a Trump-designated agency head reviews and approves them. The draft guidances and the Memorandum have already been published in the Federal Register, so comments may still be submitted; it will be up to the Trump administration to determine whether to withdraw the drafts or consider the comments. In addition, the effective dates for regulations that have been published, but have not taken effect, are to be temporarily postponed for 60 days from January 20, after which the agency/department may "consider potentially proposing further notice-and-comment rulemaking" and consult with the Office of Management and Budget Director if further action is appropriate. The Final Rule described above, which had an effective date of February 8, 2017, falls within this category, and the new effective date may now be delayed pending the administration's review.

³¹ *Id.* at 2,206.

³² *Id.* at 2,208.

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