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Client Alert

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FDA Takes Action in the Last Days of the Obama Administration to Clarify Some of Its Views on Off-Label Communications

In the last few days of the Obama Administration, the Food and Drug Administration (FDA or the Agency) issued a number of documents with implications for manufacturer communications with health care practitioners and payors. This client alert provides an overview of the following two documents:

(1) The Final Rule Revising the "Intended Use" Regulations – This final rule was issued on January 9, to clarify, among other things, the meaning of the term "intended use" in connection with FDA's authority to regulate medical products, *see* 82 Fed. Reg. 2193 (Jan. 9, 2017); and

(2) New Draft Guidance for "Consistent" Communications – This draft guidance, which is entitled, "Medical Product Communications That Are Consistent With the FDA-Required Labeling – Questions and Answers," was issued on January 17, and it addresses how the Agency will treat information that is "consistent" with, but not contained in, FDA-required labeling.

We will address the following two additional documents in separate client alerts:

(3) New Payor Communications Guidance – This draft guidance, which is entitled, "Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities: Questions and Answers," was issued on January 18; and

(4) Memorandum on Off-Label Communications – On January 19, FDA posted this memorandum to the docket associated with the public meeting that the Agency held on off-label issues in November 2016. The memorandum is entitled, "Memorandum: Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products."

Background on FDA's Off-Label Policies to Date

Under the Federal Food, Drug, and Cosmetic Act (the FD&C Act or Act), FDA has the authority to regulate articles, as drugs, devices, or

combination products, if the articles implicate the disease or the structure/function prongs of the "drug" or "device" definition in the Act – i.e., if they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of a disease or condition, or if they affect the structure or function of the body. *See* 21 U.S.C. § 321(g) and (h).

FDA's longstanding position is that, to determine a product's intended use, the Agency may consider "any relevant source of evidence," including a variety of direct and circumstantial evidence to establish "intended use." 82 Fed. Reg. at 2206. For example, in evaluating the intended use of a product, FDA often considers how the product is distributed or sold, evidence of a manufacturer's marketing plans or directions to its sales force, evidence of the well-known uses and abuses of its products, or evidence of a manufacturer's knowledge that a product is being used for an unapproved use. *See id.* Medical products that are intended for an unapproved or uncleared new use – colloquially referred to as an "off-label" use – violate the FD&C Act, and such medical products are often "misbranded." *See* 21 U.S.C. §§ 331(a), (k), 355(a), 352(f), 351(f)(1), 352(o), 360, 360c, and 360e.

FDA, however, has issued guidance documents that effectively provide safe harbors, or examples of circumstances under which off-label information can be disseminated by medical product manufacturers without being considered to be "evidence of a new intended use." These guidance documents include FDA's draft guidance entitled "Distributing Scientific and Medical Publications on Unapproved New Uses – Recommended Practices," (Reprints Guidance), which was issued in February 2014, and FDA's draft guidance entitled "Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices" (Unsolicited Requests Guidance), which was issued in December 2011. Conceptually, these draft guidance documents permit off-label information to be disseminated by medical product manufacturers in certain instances where the information is considered to be "scientific exchange," as opposed to "promotion."

However, in December 2012, the Second Circuit, in *United States v. Caronia*, 703 F.3d 149 (2d. Cir. 2012), issued a decision that challenged the notion that it is only lawful for a manufacturer to disseminate off-label information to health care practitioners if it qualifies as "scientific exchange." In that case, the Second Circuit held that the government cannot prosecute pharmaceutical manufacturers or their representatives under the FD&C Act for "speech promoting the lawful, off-label use of an FDA-approved drug." *Id.* at 169. That case involved a pharmaceutical sales representative – Alfred Caronia – who "was found guilty of conspiracy to introduce a misbranded drug into interstate commerce, a misdemeanor violation of 21 U.S.C. §§ 331(a) and 333(a)(1)." *Id.* at 152. In particular, Caronia "promoted the drug Xyrem for 'off-label use,' that is, for a purpose not approved by the [FDA]...." *Id.* On appeal, Caronia principally argued that the misbranding provisions of the FD&C Act "prohibit off-label promotion, and therefore, unconstitutionally restrict speech." *Id.* at 160. The Second Circuit reasoned that "promoting off-label drug use concerns lawful activity (off-label drug use), and the promotion of off-label drug use is not in and of itself false or misleading." *Id.* at 165. The court thus "construe[d] the misbranding provisions of the FD&C Act as not prohibiting and criminalizing the truthful off-label promotion of FDA-approved prescription drugs." *Id.* at 168.

In August 2015, in *Amarin Pharma, Inc. v. United States Food and Drug Administration*, 119 F. Supp. 3d 196, 224 (S.D.N.Y. 2015), a district court in the Second Circuit amplified the holding in *Caronia*. The *Amarin* case involved a similar First Amendment challenge. The plaintiff manufactured a triglyceride-lowering drug that FDA had approved "for one use, but doctors ha[d] widely, and lawfully, prescribed it for another." *Id.* at 198. Amarin wanted to make "truthful statements to doctors relating to [the drug's] off-label use," but FDA "threatened to bring misbranding charges against Amarin (and, presumably, its employees) if it d[id] so." *Id.* Amarin therefore filed suit against FDA to stop it from bringing an action against it. Citing *Caronia*, the *Amarin* court granted Amarin relief, concluding that the "FDA may *not* bring such an action based on truthful [off-label] promotional speech alone, consistent with the First Amendment." *Id.* at 224.

The decisions in *Caronia* and *Amarin* underscored a long-debated policy issue – namely, whether FDA should permit the dissemination of truthful and non-misleading off-label speech in more contexts to better inform health care practitioners who are making individual treatment decisions. The legal issue raised in those cases, of course, was whether FDA's existing off-label policy is consistent with the First Amendment.

In June 2014, in the wake of the decision in *Caronia*, but before the decision in *Amarin*, FDA responded to a citizen petition requesting additional clarity from FDA on its off-label policies. In that response, FDA promised "guidance that addresses unsolicited requests, distributing scientific and medical information on unapproved new uses [i.e., off-label uses], and manufacturer discussions regarding scientific information more generally, by the end of the calendar year." This guidance was expected to build on FDA's draft Reprints Guidance and draft Unsolicited Requests Guidance to answer the question of whether FDA, in the wake of *Caronia*, still believed that truthful and non-misleading off-label promotion constitutes "evidence of a new intended use" at all, and if so, in what circumstances. The latter question was essentially whether FDA, after *Caronia*, was willing to recognize additional safe harbors, or circumstances where manufacturer dissemination would not constitute "evidence of intended use."

Yet, the promised guidance never issued, presumably because it was controversial. Indeed, a provision (section 2102) in the version of the 21st Century Cures Act passed by the House of Representatives in July 2015 would have required FDA to issue the promised guidance within 18 months of the enactment of the legislation. That provision, however, was not retained in the final version of the 21st Century Cures Act signed into law in December 2016. Rather, FDA held a public meeting in November 2016 to explore the issue of whether it should change, or loosen the reins on, its off-label policy. *See* FDA Notification of Public Hearing on Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products, 81 Fed. Reg. 60,299 (Sept. 1, 2016).

Notably, in a *Federal Register* notice published today, FDA reopened the comment period for the docket related to the November 2016 public meeting for 90 days, and it added a document entitled "Memorandum: Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products." This document is accessible here, and it will be the subject of a separate client alert, which will issue shortly. Presumably, after FDA has reviewed the comments, the Agency will decide whether to issue the comprehensive off-label guidance that it promised in 2014, and if so, what its off-label policy should be, moving forward.

Despite FDA's failure to issue timely comprehensive off-label guidance, FDA has taken action in the off-label space in the very last days of the Obama Administration. Two of those actions are addressed here. The first action clarifies FDA's understanding of the impact of the decisions in *Caronia* and *Amarin* on the Agency's off-label policy, and the second action helps to clarify what types of information FDA does not consider to be "off-label" in the first place – in other words, the types of information that will *not* provide "evidence of a new intended use."

Overview of Two Recent FDA Actions in the Off-Label Space

As mentioned, FDA recently: (1) published a final rule to clarify, among other things, the meaning of the term "intended use" in connection with its authority to regulate medical products, *see* 82 Fed. Reg. 2193 (Jan. 9, 2017), and (2) issued a draft guidance entitled, "Medical Product Communications That Are Consistent With the FDA-Required Labeling – Questions and Answers."

1. Overview of the Revisions to the "Intended Use" Regulations

The final rule, issued on January 9, 2017, is entitled, "Clarification of When Products Made or Derived from Tobacco are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding

'Intended Uses'", but this client alert focuses exclusively on the rule's revision to the "intended use" regulations for drugs and devices in 21 C.F.R. §§ 201.128 and 801.4. Those regulations set out how FDA will determine the "intended use" of a product, and the new rule modifies both regulations in two major ways:

- By deleting language that stated: "[I]f a manufacturer knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a drug which accords with such other uses to which the article is to be put."

- By adding language that states: "[I]f the totality of the evidence establishes that a manufacturer objectively intends that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than ones for which it is approved (if any), he is required . . . to provide for such drug adequate labeling that accords with such other intended uses."

Notably, the added language did not appear in FDA's proposed rule, although the deletion did. *See* 80 Fed. Reg. 57756 (Sept. 25, 2015).

In its explanation for the revised rule, FDA states that the intent is to clarify that the Agency would not regard a drug, device, or combination product manufacturer as intending an unapproved use (i.e., off-label use) based *solely* on the manufacturer's knowledge of the off-label use, *e.g.*, based solely on a manufacturer's knowledge that doctors are using or prescribing the product for a use that has not been approved or cleared. *See* 82 Fed. Reg. at 2206. Instead, the Agency plans to examine all relevant evidence – which could include whether the manufacturer knows that doctors are prescribing or using a drug or device for an unapproved or uncleared use – in evaluating whether there is sufficient evidence that the manufacturer intends that unapproved or uncleared use. *See id.* As mentioned, if FDA makes the requisite finding for a given product, the Agency would consider that product to be violative of the FD&C Act.

In explaining its new rule, FDA also acknowledged that several commenters asserted that its "intended use" regulations ran afoul of the First Amendment, especially in light of the decisions in *Caronia* and *Amarin.* However, the Agency did not agree with that assertion, and stated that those cases do not prevent FDA from considering speech as "evidence of intended use" even when it is truthful and non-misleading. *See id.* at 2209. According to FDA, the Agency's "consideration of speech as evidence of intended use . . . advances substantial public health interests relevant to" a First Amendment analysis. *Id.* Nevertheless, FDA noted that it was separately considering "rules and policies relating to firm communications regarding unapproved uses of approved/cleared medical products," alluding to the comments submitted to the docket related to the November 2016 public meeting. *Id.* at 2209; *see also* FDA Notification of Public Hearing on Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products, 81 Fed. Reg. 60,299 (Sept. 1, 2016).

2. Overview of the New Draft Guidance for "Consistent" Communications

On January 17, 2017, FDA issued a draft guidance entitled, "Medical Product Communications That Are Consistent With the FDA-Required Labeling – Questions and Answers." As mentioned, this draft guidance is not the one that was promised by FDA in its citizen petition response in 2014, and it does not contain any new policies related to unapproved/uncleared uses of medical products, i.e., off-label uses. The draft guidance addresses a wholly separate question – namely, what types of information constitute, or do not constitute, "off-label" information in the first place. The issuance of this draft guidance underscores the fact that the entire time that FDA and the regulated community have been debating the circumstances in which manufacturer dissemination of off-label information

should (or should not) constitute "evidence of a new intended use," the actual definition of "off-label" was never clear.

In the absence of clarity on the meaning of the term "off-label," and indeed the term "on-label," many previously have suggested that: (1) the term "on-label" should refer only to information in FDA-required labeling, (2) the term "off-label" should refer only to information that could trigger the need for a supplemental marketing application (e.g., in the context of drugs, for example, information that recommends or suggests that a drug may be used to treat a new indication, or a new subpopulation, or information that recommends or suggests a new dosing regimen or a new route of administration), and (3) the term "out-of-label" should refer to all other information about a medical product.

To be clear, the draft guidance does not adopt these definitions, nor does it even purport to define the terms "on-label," "out-of-label," or "off-label" at all. But, the draft guidance specifically addresses how the Agency will treat information that: (1) is *not* contained in the FDA-required labeling (i.e., information that is not "on-label" based on the suggested definitions above), but (2) is *consistent* with FDA-required labeling. Conceptually, it may be helpful to think of this information as "out-of-label" information that is consistent with FDA-required labeling. Notably, the draft guidance proposes to treat this information differently from "off-label" information – in that FDA will not consider the dissemination of "out-of-label" information that is consistent with FDA-required labeling, alone, to be "evidence of a new intended use."

The draft guidance lists three factors to help stakeholders distinguish between "out-of-label" information that is *consistent* with FDA-required labeling and "out-of-label" information that is *inconsistent* with that labeling. According to FDA, if the information in the communication fails to satisfy any one of these factors, FDA would not consider the communication to be *consistent* with FDA-required labeling.

- Factor 1 – How the information in the communication compares to the information in FDA-required labeling. With respect to this factor, FDA will consider information to be consistent with FDA-required labeling if: (1) representations or suggestions in the communication relate to the same indication as the one reflected in the product's FDA-required labeling; (2) the patient population represented or suggested in the communication is the same as the approved/cleared patient population reflected in FDA-required labeling; (3) the representations/suggestions in the communication do not conflict with the use limitations or directions for handling, preparing, and/or using the product reflected in FDA-required labeling; and (4) the representations/suggestions about the product do not conflict with the recommended dosage or use regimen, route of administration, or strength(s) (if applicable) set forth in FDA-required labeling.

- Factor 2 – Whether the representations/suggestions in the communication increase the potential for harm to health relative to the information reflected in the FDA-required labeling. With respect to this factor, FDA is much more likely to determine that an "out-of-label" communication is consistent with FDA-required labeling if the "out-of-label" communication does not alter the benefit-risk profile of the product in a way that may result in increased harm to health.

- Factor 3 – Whether the directions for use in FDA-required labeling enable the product to be safely and effectively used under the conditions represented/suggested in the communication. If the answer is "no," FDA would likely determine that the "out-of-label" communication is not consistent with FDA-required labeling.

See "Medical Product Communications That Are Consistent With the FDA-Required Labeling – Questions and Answer," at 3-5.

The draft guidance also provides the following examples of "out-of-label" information that could be consistent with FDA-required labeling:

- Information based on a comparison of the safety or efficacy of a medical product for its approved or cleared indication to another medical product's same approved or cleared indication;
- Information that provides additional context about the adverse reactions associated with the approved or cleared uses of the product;
- Information about the onset of action of the product for its approved or cleared indication and dosing or use regimen;
- Information about the long-term safety and/or efficacy of products that are approved/cleared for chronic use;
- Information about the effects or use of a product in specific patient subgroups that are included in its approved/cleared patient population;
- Information concerning the effects of a product that comes directly from the patient;
- Information concerning product convenience; and
- Information that provides additional context about the mechanism of action described in FDA-required labeling.

Id. at 6–8. Notably, FDA's stance here, particularly with regard to information regarding the onset of action, the mechanism of action, patient-reported outcomes, and even certain comparative claims, strikes us as more permissive than FDA's historical approach. *See, e.g.*, 21 C.F.R. § 202.1(e)(6), (7).

In addition, the draft guidance states that communications that lack appropriate substantiation are likely to be false or misleading, and it proposes a substantiation standard for "out-of-label" information that is consistent with FDA-required labeling. According to FDA, such "representations or suggestions made by firms about their products need to be grounded in fact and science and presented with appropriate context." *Id.* at 8. FDA also states that any data, studies, or analyses "should be scientifically appropriate and statistically sound to support the representations or suggestions made in the communication." *Id.* This "scientifically appropriate and statistically sound" substantiation standard departs from, and strikes us as lower than, FDA's "substantial evidence" standard, which is required to support FDA approval of new indications and conditions of use, *see* 21 U.S.C. § 355(d), and indeed to prevent certain advertisements that reference information not contained in FDA-required labeling from being unlawful, *see, e.g.*, 21 C.F.R. § 202.1(e)(6), (7).

Finally, the draft guidance recommends that companies make certain disclosures in connection with the "out-of-label" communications discussed in the draft to prevent the Agency from perceiving the communications to be false or misleading. Specifically, the Agency states that the communications should:

- Accurately represent any study results or other data and information that the firm relied upon to support its communication, and disclose material aspects of the study design and methodology (e.g., the type of study, the study's objectives, product dosage/use regimens used, controls used, and the studied patient population), and material limitations related to the study design or methodology;

- Disclose and contextualize unfavorable or inconsistent findings; and
- As appropriate, disclose information from FDA-required labeling to help contextualize the communication.

Id. at 10–11.

Implications of These Two Recent FDA Actions

As summarized above, FDA's existing off-label policy has been controversial for years, and the decisions in *Caronia* and *Amarin* only heightened the debate. The two recent FDA actions discussed herein articulate several of the Obama Administration's positions in this space.

The preamble to the final rule clearly articulates that FDA still believes, post *Caronia* and *Amarin*, that the Agency may consider "any relevant source of evidence," including both manufacturer knowledge of off-label use and truthful and non-misleading off-label promotion, to be "evidence of a new intended use." *See* 82 Fed. Reg. at 2206. The final rule thus signals that the Agency has not given up on its long-held position in this regard despite recent losses in court. Conveying that message may be the most significant function of the final rule, because the revisions to the "intended use" regulations, and the explanations for them in the preamble, do not actually change FDA's policy. Rather, the revisions conform the text in the regulations to more accurately reflect how the Agency currently applies them. As a result, the "intended use" regulations continue to permit prosecution for "misbranding" based on truthful, non-misleading speech, and that application of the regulations continues, in our view, to violate the First Amendment. Accordingly, companies should continue to make forceful First Amendment arguments of the type that prevailed in *Caronia* and *Amarin* both offensively, in declaratory judgment actions, and defensively, in lawsuits brought by the government.

The implications of the draft guidance, "Medical Product Communications That Are Consistent With the FDA-Required Labeling – Questions and Answers," are arguably more interesting. FDA seems to be seeking to narrow the scope of the debate. The key debate is over whether truthful and non-misleading "off-label" information about a medical product can be responsibly disseminated to health care practitioners without "misbranding" the product. FDA, in this draft guidance, clarified that "out-of-label" information that is consistent with FDA-required labeling, under the terms of the draft guidance, does not need to be part of that debate. The question that remains, for the purposes of this draft guidance, is whether FDA appropriately narrowed the scope of the "off-label" debate, or whether the scope of the "off-label" debate should be narrowed further, from both a legal and a policy perspective.

Should, for example, the terms "on-label," "off-label," and "out-of-label" be more clearly defined, as discussed above? And, should all "out-of-label" information *not* constitute "evidence of a new intended use" and be subject to the "scientifically appropriate and statistically sound" substantiation standard? Such changes, or indeed, other changes to the policy in the draft guidance, as applied, may be more likely to survive judicial scrutiny than the policy articulated in the draft guidance, to the extent that they would restrict less speech. The comment period on the draft guidance is open for 90 days from today (i.e., until April 19, 2017).

Finally, it is worth noting that the timing of these actions in the last few days of the Obama Administration may serve to provoke counter actions by the incoming Trump Administration, or indeed, by Congress. FDA has had years to issue meaningful and sensible guidance about the dissemination of off-label information.

Doing so could have enabled the Agency to get in front of the issue and head off losses in court. Now, over four years after *Caronia*, a year and a half after *Amarin*, and in the final moments of the Obama Administration, FDA has issued this final rule and draft guidance. The final rule, however, does not change the "intended use" regulations in substance and appears primarily intended to signal to stakeholders that the Agency is not yet ready to back down from its positions that were defeated in court in *Caronia* and *Amarin*. And the draft guidance is limited to what may be thought of as a subset of "out-of-label" information; it does not address the dissemination of information about off-label uses. These two newly-issued documents thus do not even grapple with the legal problems that caused the government's defeats in *Caronia* and *Amarin*, let alone solve those problems. The long-running legal and policy debate over the dissemination of off-label information will continue, and the Trump Administration will have its own opportunity to weigh in.

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