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FDA Proposes New Rule Modifying its "Intended Use" Regulations

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Yesterday, FDA published a proposed rule amending its medical product "intended use" regulations in an effort to "provide direction and clarity to regulated industry and other stakeholders."[1] If finalized, the rule would amend FDA's drug and device regulations that describe the types of evidence relevant to determining whether a product is intended for use as a drug or a device under the Federal Food, Drug, and Cosmetic Act (FD&C Act), or intended for a "new" unapproved or uncleared use—colloquially referred to as an "off-label" use.[2]

This is the latest development in a long-standing back and forth between FDA and industry. By way of background, FDA issued a proposed rule in 2015[3] and a final rule in 2017[4] revising the language of its "intended use" regulations in an attempt to conform the regulations to the agency's existing practices.[5] Although the revisions at that time did not, according to FDA, reflect a change in FDA's approach conceptually, the changes were controversial. In particular, industry was concerned about language in the regulation that indicated that FDA would use a "totality of the circumstances" test to determine if companies intended for their medical products to be used "off-label." As such, the final rule elicited a petition from industry requesting that the agency reconsider the revisions. In response, FDA delayed the effective date of the final rule and reopened the docket for public comment.[6] On March 18, 2018, FDA delayed the effective date of the revised "intended use" regulations until further notice to allow time for full consideration of the comments that had been submitted.[7] With today's proposed rule, FDA is trying again.[8]

Below, Section I provides a "red-line" showing the proposed changes to the "intended use" regulations; Section II explains the impact of the proposed changes to the regulations and the impact of FDA's statements in the preamble to the proposed rule; and Section III provides key take-aways.

I. Proposed Revisions to the "Intended Use" Regulations

To fully illustrate the changes, we have provided a "red-line" of the existing "intended use" regulation for *drugs*, showing the changes that would be made if the proposed rule is finalized. The changes to the "intended use" regulation for devices are almost identical.

> The words intended uses or words of similar import in §§ 201.5, 201.115, 201.117, 201.119, 201.120, and 201.122, and 1100.5 of this chapter refer to the objective intent of the persons legally responsible for the labeling of an article (or their representatives) ~~of drugs~~. The intent may be shown ~~is determined~~ by such persons' expressions, the design or composition of the article, or ~~may be shown~~ by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. ~~It~~ Objective intent may be shown, for example, by ~~the~~ circumstances ~~that~~ in which the article is, with the knowledge of such persons or their representatives, offered or ~~and~~ used for a purpose for which it is neither labeled nor advertised; provided, however, that a firm would not be regarded as intending an unapproved new use for an approved drug based solely on that firm's knowledge that such drug was being prescribed or used by health care providers for such use. The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer. If, for example, a packer, distributor, or seller intends an article for different uses than those intended by the person from whom he or she received the article ~~drug~~, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses. ~~But if 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.~~

II. Modifications and Effects of the Proposed Rule and Its Preamble

In FDA's press announcement regarding the proposed rule, the agency emphasized that, like the 2015 proposed rule and 2017 final rule, today's proposed "intended use" rule does not reflect a change in FDA's policies and practices but rather is intended to "clarify the regulatory language describing the types of evidence [the agency] considers relevant to determining a product's intended use."[9] In particular, by revising 21 C.F.R. §§ 201.128 and 801.4, the proposed rule is intended to "clarify an important point" and indeed, the most serious concern raised by industry, "that a firm's knowledge that a health care provider has prescribed or used an approved or cleared medical product for an unapproved use, standing alone, is not sufficient to establish the product's intended use."[10] Significantly, however, FDA is not actually giving up new ground here. Rather, the agency is seeking to codify a long-standing policy. In 2009, in an affidavit submitted in *Allergan v. United States of America*, the agency conceded "FDA would not ordinarily regard a manufacturer as intending an off-label use for an approved product based solely on the manufacturer's knowledge that an approved product was being prescribed by doctors for such use, and even if the sponsor provided scientific articles about such use."[11]

The rule also proposes to insert in 21 C.F.R. §§ 201.128 and 801.4 a reference to 21 C.F.R. § 1100.5, which describes when a product made or derived from tobacco that is intended for human consumption will be subject to regulation as a drug, device, or combination product.[12] With this change, the agency seeks to "clarify the interplay between the drug and device intended use regulations and FDA's regulations governing products that are made or derived from tobacco and intended for human consumption."[13]

Additionally, the proposed rule also proposes changes to clarify and reinforce that "intended use" can be based on any relevant source of evidence, including "the design or composition of the article."[14] FDA, in the preamble, also

expressly states that relevant sources of evidence include "a variety of direct and circumstantial evidence."[15] For illustrative purposes, FDA also provides examples of types of evidence that are "relevant to establishing intended use," including:[16]

- *Express Claims and Representations*—such as labeling claims and representations, advertising matter, and oral or written statements by persons responsible for the labeling, or their representatives.
- *Implied Claims*—such as suggestive product names; statements that imply an "intended use," such as "For best results use approximately 30-45 minutes prior to engaging in sexual intercourse"; and representations that a product contains a particular ingredient to imply a physiological effect, such as "aspirin" or "sildenafil."
- *Product Characteristics and Design*—such as the known physiological effects (medical or recreational) of a product that is unapproved for any medical use; the known (recreational or medical) use of a product that is unapproved for any medical use; and the product's design and technical features, like a stent that is specifically sized for a use that is different from the purported use.
- *Circumstances of the Sale or Distribution*—including to whom and for whom the products are offered, such as the repeated detailing and sampling to healthcare providers whose patient population does not fall within the product's approved population; and the circumstances and context surrounding the sale, such as the repackaging of bulk product into small plastic bags, and using personal, not business, emails and addresses for communications and deliveries.

The proposed rule also provides examples of evidence that, standing alone, are *not* determinative of "intended use," including:[17]

- *Knowledge, Alone or in the Context of "Safe Harbors," of Health Care Providers (HCPs) Prescribing or Using an Approved Product for an Unapproved Use*, such as:
  - A pharmaceutical firm that tracks sales and distribution metrics notes that one of its products that is approved only for use in adults is also being ordered by and distributed to many medical practices that only treat pediatric patients. The firm does not direct its sales or marketing staff to disseminate samples or information about the product to pediatric practices.
  - A pharmaceutical firm is aware that one of its oncology products approved only for use in adults is being ordered by and distributed to many medical practices that treat only pediatric oncology patients. The National Comprehensive Cancer Network clinical practice guidelines (CPG) recommend the firm's product for pediatric patients. The firm distributes copies of the CPG in accordance with FDA's revised draft guidance, "Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices" (Feb. 2014), thus falling within FDA's "safe harbor," and does not direct sales or marketing to target pediatric practices.
- *Dissemination of Safety or Warning Information about an Unapproved Use to HCPs*—An unapproved use of a firm's approved drug is broadly accepted by the medical community and the firm has submitted an efficacy supplement to add the unapproved use to the drug's labeling. The boxed warning and risk evaluation and mitigation strategy (REMS) materials for the drug warn of potential risks related to the unapproved use in general terms, but the firm disseminates additional specific safety and warning information to HCPs to minimize the risk to patients receiving the drug for the unapproved use. The safety and warning information does not expressly or implicitly promote the efficacy of the unapproved use.

- *"Following" the Social Media Account of a Nonprofit Without Comment*—A firm's official social media account "follows" the social media account of a non-profit that supports patients with a rare disease for which there is no FDA-approved treatment. The firm is in the process of investigating one of its FDA-approved products for use in the rare disease that the non-profit supports. The nonprofit account disseminates messages about charity events, scientific conferences, support groups, and rare disease research and development, but the firm account does not make any comments or otherwise endorse any specific posts on the non-profit account.
- *Internal Sales Projections that Include Sales from a Widely Accepted Unapproved Use*—During an internal sales meeting, a firm's CEO displays a slide of internal sales projections for its approved product. The slide reflects potential sales for an unapproved use that is widely recognized as the standard of care.
- *Corporate Filings or Submissions to the U.S. Securities and Exchange Commission (SEC)*—A firm makes corporate filings or submissions to the SEC that include required disclosures of development activities or potential or actual sales for an unapproved use.
- *Summaries of Clinical Trial Results Prepared Exclusively for Participants*—Following a clinical trial, a firm prepares a plain-language summary of the aggregated clinical trial results and provides the summary solely to the trial participants to acknowledge their contributions to scientific and medical advancement (not to inform prescribing and use decisions). The summary provides a factual, balanced, and complete presentation of the trial results, including relevant safety information and study limitations, but does not make any conclusions about safety or effectiveness. The summary also includes a clear statement that the product or use has not been approved by FDA.

III. Key Takeaways

The biggest change that the proposed rule would make, if it is finalized, is that it would revise the existing text of the "intended use" regulations to make clear that the agency would not determine that a company is marketing a product off-label based on knowledge of off-label use "alone." Notably, however, with this proposed change, FDA is not giving "manufacturer knowledge of off-label use" a free-pass. Rather, based on the revisions, FDA would use manufacture knowledge of off-label use—*only* in addition to other evidence of objective intent—when assessing whether a product is *intended* for off-label use. As mentioned, this is not a true policy change. If the proposed revision is finalized, it would simply codify a policy that FDA announced in 2009, in the course of litigation in *Allergan v. United States of America*.

However, the proposed rule and its preamble are important because, like an FDA guidance, they show FDA's current thinking on the types of evidence that constitute—and do not constitute—evidence of a new "intended use." In the proposed rule and its preamble, FDA reminds stakeholders that the evaluation of "intended use" is specific to the unique circumstances of each case. Where a single piece of evidence may be dispositive in some cases, other cases may rely on several combined elements to establish a product's "intended use." FDA's examples of evidence that, standing alone, are not determinative of "intended use," are helpful in guiding company activities; however, there are a range of activities, not enumerated in the proposed rule, that must be carefully considered in the aggregate when navigating the risk of a new "intended use." Many of the examples in the proposed rule provide new insights into the agency's thinking on certain activities, including the dissemination of safety information related to an unapproved use, dissemination of summaries of clinical trial results to study participants, and "following" a social media account—that may not "alone" be determinative of a product's "intended use". However, those effective safe harbors are limited to the extent that they hinge on being non-promotional communications.

Significantly, the question remains as to whether this proposed rule will prove to be as controversial as the 2017 final rule that never went into effect. Even though FDA, with this proposal, has moved away from the "totality of the circumstances" language that was so controversial in the 2017 final rule, FDA in its new proposed rule, and in the preamble to it, still makes clear that it will be evaluating—advertising, labeling, any other written or oral statements made by the entity responsible for labeling, "the design or composition of the article," and a variety of direct and circumstantial evidence—when it makes determinations as to whether a company intends for its product to be used "off-label." In other words, even though FDA is not expressly articulating a "totality of circumstances" test in the regulations, it is still taking a lot of different circumstances into account. Therefore, those that believe that the agency should take into account *only* express claims in labeling and advertising when evaluating whether a company intends for its product to be used "off-label," may still have concerns.

FDA is accepting comments on the proposed rule for 30 days, until October 23, 2020. King & Spalding can help your firm prepare comments on the proposed rule for submission to the agency or answer any questions you may have about this new proposed regulation.

[1] FDA, Proposed Rule, *Regulations Regarding "Intended Uses,"* 85 Fed. Reg. 59,718 (Sep. 23, 2020) [hereinafter "*2020 Proposed Rule*"].
[2] *Id*.
[3] FDA, Proposed Rule, *Clarification of When Products Made or Derived from Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses,"* 80 Fed. Reg. 57,756 (Sep. 25, 2015).
[4] FDA, 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).
[5] *2020 Proposed Rule*, 85 Fed. Reg. at 59,719-20.
[6] *See generally* FDA, *Clarification of When Products Made or Derived From Tobacco Are Regulated as Drugs, Devices, or Combination Products*, Docket No. FDA-2015-N-2002, https://beta.regulations.gov/docket/FDA-2015-N-2002.
[7] *See* FDA, Partial Delay of Effective Date, *Clarification of When Products Made or Derived From Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses,"* 83 Fed. Reg. 11,639 (Mar. 16, 2018).
[8] *See id*.

[9] *See* FDA, Press Release, *FDA Clarifies Types of Evidence Relevant to Determining the "Intended Use" of FDA-Regulated Products* (Sep. 22, 2020) [hereinafter "*Press Release*"], https://www.fda.gov/news-events/press-announcements/fda-clarifies-types-evidence-relevant-determining-intended-use-fda-regulated-products; *see also 2020 Proposed Rule*, 85 Fed. Reg. at 59,718.
[10] *Press Release* at 1.
[11] Declaration of Robert Temple, M.D., *Allergan v. United States of America*, filed in the U.S. District Court of the District of Columbia, on October 1, 2009, Case No. 1:09-cv-01879-JDB (on file).
[12] *See 2020 Proposed Rule*, 85 Fed. Reg. at 59,720.
[13] *See id*.
[14] *See id*. at 59,729.
[15] *Id*. at 59,721.
[16] *See id*. at 59,724-25.
[17] *See id*. at 59,725-26.