FDA Finalizes "Intended Use" Regulations

Final Rule Closely Resembles Proposed Rule and Codifies Longstanding Agency Policies

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On August 2, 2021, the U.S. Food & Drug Administration ("FDA" or "the Agency") published a final rule amending its medical product "intended use" regulations in an effort to provide direction and clarity to regulated industry and other stakeholders. The rule amends FDA's drug and device regulations that describe the types of evidence that FDA will consider when 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.[1] Despite the change, the Agency clarifies several times in its responses to comments that the final rule does not represent a change in FDA policy, but merely codifies longstanding Agency practices for identifying a product's intended use. The final rule will take effect September 1, 2021.

The final rule closely resembles the proposed rule that FDA issued on September 23, 2020.[2] Indeed, as FDA describes in its final rule, the only change is that FDA "modified the codified language of the intended use regulation for medical devices to clarify its applicability to devices that are approved, cleared, granted marketing authorization, or exempted from premarket notification."[3] We published a Client Alert analyzing the proposed rule in detail, which is available here.

FDA's finalization of this rule ends a long-standing back and forth between FDA and industry. FDA issued a different proposed rule in 2015[4] and a different final rule in 2017[5] in its first attempt to revise the language of its "intended use" regulations to better conform the regulations to the Agency's existing practices.[6] 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.[7] 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.[8] Then, as described above, FDA issued a proposed rule on September 23, 2020, which the Agency finalized in nearly identical form on August 2, 2021.

FINAL 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 made by the final rule. 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, 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~~.

FDA'S RESPONSES TO COMMENTS IN THE FINAL RULE

Approximately 15 comments on the proposed rule were submitted to the docket by various industry trade organizations, consumer advocacy groups, and individuals. FDA grouped comments into nine categories and responded accordingly. Below is a summary of the comments and FDA's responses. Overall, FDA rejected nearly every comment, but, in the process, provided potentially helpful insights into the Agency's thinking on key issues.

- *Comments and Responses Regarding Statutory and Regulatory Authority*: FDA rejected comments suggesting that it lacked the required legal authority to determine a product's intended use based on the wide-ranging factors identified in the final rule.
    - One comment asserted that evidence of intended use is limited to promotional claims that have been made in the marketplace and may not be derived from "any relevant source," including "circumstances surrounding distribution."[9] FDA disagreed, arguing that nothing in the statute or the existing regulation requires an exclusively claims-based approach to intended use.[10] FDA also pointed to legislative history showing that Congress intended to allow FDA to consider use of a

product in determining whether it is intended as a drug or device.[11] Then, FDA cited a number of cases in favor of its position and a general lack of case law cutting the other way.[12] Another comment asserted that the phrase "any relevant evidence" should be understood to refer only to evidence of promotional claims under the statutory interpretation principle of *ejusdem generis*.[13] FDA responded by again citing the numerous court decisions conflicting with the commenter's position.

- One comment asserted that FDA's position was an "alternative, novel interpretation with which FDA has flirted from time to time in the past."[14] Again, the Agency disagreed, stating that it has "steadfastly maintained for decades that, in determining a product's intended use, the Agency may look to any relevant source of evidence, including a variety of direct and circumstantial evidence."[15]
- Several comments suggested that the government could use other regulatory tools to regulate intended uses of a product that are not set forth in promotional claims.[16] For example, one commenter specifically argued that FDA should use its food and dietary supplement regulatory authorities to regulate any product that is not promoted as a drug.[17] FDA disagreed, stating that its "position regarding evidence relevant to establishing intended use helps protect the public health" by helping to "ensure that [the Agency] can help curb the distribution of dangerous and fraudulent products."[18] FDA further stated that its regulatory authority over foods and dietary supplements is "not a substitute for FDA's medical product authorities that include an intended use determination." The Agency also reiterated that it "intends to continue considering the full range of evidence relevant to determining intended use."[19]
- One comment argued that the rule should clarify that only promotional conduct will be considered in determining a product's intended use. FDA declined the suggestion, stating that non-promotional activity can be relevant to determining a product's intended use.[20] FDA provided specific examples of non-promotional activity that can serve as evidence of intended use such as "a stent . . . specifically sized for a use that is different from the purported use" or "a spacer that the manufacturer claims can be used to elute one liquid, but is in fact designed with holes that are sized to elute a more viscous substance that contains a different active ingredient."[21] With these examples, FDA also provided some guidance as to when it might regulate a product as a drug or device based on its "design or composition."

- *Comments and Responses Regarding the Design or Composition of an Article*: FDA rejected comments suggesting that it should not consider a product's design or composition in determining its intended use.
  - Several comments argued that FDA should reconsider relying on a product's "design or composition" as evidence relevant to establishing intended use. FDA disagreed with the comments and declined to remove "design or composition" from the codified language.[22] By way of example, FDA stated that it "may consider the design or composition of a product, which includes product characteristics, when determining whether the product is 'intended to affect the structure or any function of the body.'"[23] The Agency also clarified that "the addition of the phrase 'design or composition' to the codified [language] reflects FDA's longstanding and current policy that these are relevant to intended use."[24]
  - Some comments suggested that consideration of "design or composition" might inhibit technological advancements by discouraging manufacturers from designing products with multiple uses.[25] FDA

disagreed, stating that reliance on a product's design or composition to determine its intended use simply codifies long standing FDA policy which has not disincentivized innovation.[26]

- *Comments and Responses Regarding the First Amendment*: FDA rejected comments that argued that the Agency's intended use regulations run afoul of the First Amendment.
    - One comment stated that the rule is suspect under the First Amendment because it identifies potentially truthful speech as evidence relevant to establishing intended use. FDA rejected this comment, arguing that: (1) the regulations do not directly regulate speech; (2) the categorical exclusion of all truthful speech from regulatory review would undermine FDA's ability to promote and protect the public health through premarket review of medical products; (3) courts have consistently upheld FDA's reliance on speech as evidence of intended use under the First Amendment; and (4) FDA's regulation passes scrutiny under *Central Hudson* because it directly advances and is appropriately tailored to achieve, substantial public health interests.[27]
- *Comments and Responses Regarding the Fifth Amendment*: FDA rejected comments that argued that the Agency's intended use regulations run afoul of the Due Process Clause of the Fifth Amendment.
    - Some comments argued that FDA's regulation violates the Fifth Amendment because the regulation does not adequately draw "boundaries between permissible and impermissible communications" and is, therefore, unconstitutionally vague.[28] FDA rejected these arguments, citing Supreme Court holdings stating that "perfect clarify and precise" guidance are not required by the Fifth Amendment and that use of an "intent standard does not render a statute unconstitutionally vague."[29] FDA also argued that its regulations and positions on "intended use" have remained relatively unchanged over a period of decades and that "medical product manufacturers have shown little difficulty in understanding how these regulations are applied."[30]
- *Comments and Responses Regarding Definitions*: FDA accepted comments suggesting that 21 C.F.R. § 801.4 should be revised to expressly include devices that are legally marketed without approval or clearance, such as a device exempt from premarket notification or a device granted marketing authorization through, for example, a *de novo* application. FDA, however, rejected other comments related to definitions.
    - Some comments suggested clarifying and defining the terms "intended use" and "indications for use." One such comment requested that FDA adopt definitions used in other FDA regulations and guidance documents and distinguish the terms when used as part of a substantial equivalence determination for a device from the intended use regulations for drugs. FDA disagreed with these comments, explaining that they were beyond the scope of the rulemaking.[31]
    - Several commenters suggested that the definition of "intended use" applicable to devices should be amended to clarify that the definition applies to 510(k)-exempt devices which are not "approved or cleared medical products" or "approved or cleared medical uses." FDA agreed with this comment and revised the definition by adding the phrase "granted marketing authorization, or exempt from premarket notification" to the fourth sentence of § 801.4."[32]
    - Some comments suggested that FDA should define the terms "unapproved new use for an approved or cleared" and "unapproved use of an approved product." FDA rejected these comments, on the belief that defining such terms was not necessary.[33]

- Some comments suggested that FDA should expressly include "laboratorians" in the definition of "healthcare provider." FDA explained that the Agency's definition "healthcare provider" is non-exhaustive and may include some State-authorized individuals with certain roles in a laboratory.[34]

- *Comments and Responses Regarding "Safe Harbors"*: FDA rejected comments suggesting that the Agency should create enumerated safe harbors within the definition of "intended use."
  - Some comments suggested a safe harbor for "scientific exchange" that would expressly permit discussions with healthcare providers about investigational uses, discussions held in the course of providing training or demonstrations to healthcare providers, market research about unapproved uses, and communications related to the collection of postmarket data. Another comment urged FDA to codify its "policies regarding manufacturer communication of scientific and medical information."[35] FDA declined to codify any safe harbors but reiterated again that "this rule, as proposed and as finalized, does not reflect a change in FDA's policies and practices regarding the types of firm communications that ordinarily would not, on their own, establish a new intended use."[36] FDA did opine, however, that if "all scientific exchange were excluded from determinations of intended use, companies might have an incentive to create and promote new intended uses for marketed products based on incomplete or otherwise flawed data."[37] Still, the Agency recognized "the importance of scientific exchange, including information regarding unapproved uses of products that healthcare providers may choose to take into account when making professional judgments regarding the use of medical products that are approved, cleared, granted marketing authorization, or exempted from premarket notification."[38]

- *Comments and Responses Regarding Examples*: FDA rejected comments requiring that the Agency provide examples to illustrate its thinking.
  - One comment requested that FDA clarify that "repeated proactive detailing" would not create a new intended use if the firm's communications with the healthcare professionals are consistent with the approved labeling. FDA declined, stating that it did not believe the proposed clarification was warranted, reiterating that the "intended use regulations do not reflect a change in FDA's policies and practices, including as articulated in various guidance documents."[39]
  - Several comments requested that FDA describe the intended use framework from the device industry perspective and provide additional device-specific examples. FDA provided a few additional examples in response to these comments, including that the following actions could cause the Agency to determine that a product is intended for use as a device: (1) marketing a medical device with a name that implies a use to affect a particular organ or system of the body; (2) designing a non-vascular stent with a coating known to change calcification of blood vessels; and (3) marketing a device that uses ultrasonic waves as a therapeutic massager, despite the fact that ultrasonic waves do not physically massage tissue but rather affect the underlying tissue through a sonic mechanism.[40]

- *Comments on Codified Text and FDA Responses*: FDA declined certain comments suggesting that it amend the proposed language.
  - One commenter argued that FDA should delete the word "solely" from the regulation's instruction that a firm would not be regarded as intending an unapproved use for an approved product "based solely on that firm's knowledge that such drug or device was being prescribed or used by healthcare

providers for such use."[41] The commenter argued that this phrasing suggests that a firm's "knowledge of unapproved use could be used in combination with other factors to determine the intended use of a product." FDA declined to adopt the commenter's suggestion, confirming that the Agency might consider such evidence but would not find an unapproved use for an approved product based on a firm's knowledge of unapproved uses alone. FDA reiterated this point in response to another comment stating that "both legislative history and the case law support reliance on actual use by healthcare providers as relevant to intended use."[42]

- *Comments Recommending that FDA Expand the Scope of This Rulemaking*: FDA rejected numerous comments urging the Agency to expand the scope of this rulemaking beyond the scope of the proposed rule.
    - One comment urged FDA to conduct a comprehensive review of regulations and adopt a regulatory approach to manufacturer speech consistent with "Principles on Responsible Sharing of Truthful and NonMisleading Information About Medicines with Health Care Professionals and Payers."[43] FDA declined both of these suggestions because a scope expansion "would potentially delay FDA's clarification of its regulations on intended use."[44]
    - One comment requested that FDA acknowledge that healthcare providers may prescribe and use approved/cleared medical products for unapproved uses when they judge that the approved use is medically appropriate for their patients and that manufacturers are not required to confirm the nature of a healthcare provider's planned use for an approved medical product before distributing such product to the healthcare provider. FDA reiterated that its "longstanding position is that the Agency does not consider a firm's knowledge that a healthcare provider has used or prescribed its medical product that is approved, cleared, granted marketing authorization, or exempted from premarket notification for an unapproved use, by itself, as sufficient to establish the intended use element of a prohibited act based on failing to meet applicable premarket requirements for that use or failing to provide adequate directions for use."[45]

KEY TAKEAWAYS

FDA states repeatedly in response to comments that the final rule does not represent a change in Agency policy, but merely codifies FDA's longstanding approach to the issue of intended use. Still, the changes enacted by the final rule and FDA's explanations thereof in the preamble to the rule are a reflection of the Agency's latest thinking and may provide new tools for FDA to carry out its enforcement priorities.

The biggest takeaway is that the final rule explicitly clarifies 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."[46] As discussed in our previous client alert regarding the proposed rule, though, FDA is not suddenly giving "manufacturer knowledge of off-label use" a free-pass. Rather, 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. This is not a true policy change. Instead, the final rule simply codifies a policy that FDA announced in 2009, in the course of litigation in *Allergan v. United States of America*.[47]

The second key change is that the final rule explicitly codifies, for the first time, that FDA will consider a product's design or composition in determining its intended use. Although this new language does not reflect a change in policy, it may provide a new regulatory tool for FDA to carry out enforcement against medical products masquerading as consumer goods. Needless to say, on the consumer goods front, the final rule also clarifies that FDA's intended use regulations will apply to determinations of whether a tobacco-derived product is intended for use as a drug or device.

Although FDA's final rule moves away from the controversial 2017 final rule, which would have allowed FDA to assess intended use based on the "totality of the circumstances," the Agency still makes clear that it will be evaluating a range of evidence—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 how a company intended for its product to be used, including "off-label" use. In other words, even though FDA is not expressly articulating a "totality of circumstances" test in the regulations, its assessment of intended use will still consider a range of circumstances.

Indeed, the preamble in FDA's proposed rule is still instructive as to the types of evidence that the Agency considers most relevant to a product's intended use. As we described in our client alert on the proposed rule, FDA will focus on:

- 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.

In conclusion, determining a product's "intended use" will continue to be a fact-intensive analysis. FDA will continue to consider all relevant evidence as the final rule merely codifies longstanding Agency policy. If you have any questions about how the final rule might affect your business, King & Spalding stands ready to assist.

[1] FDA, Final Rule, *Regulations Regarding Intended Uses*, 86 Fed. Reg. 41383, 41384 (Aug. 2, 2021).
[2] FDA, Proposed Rule, *Regulations Regarding Intended Uses*, 85 Fed. Reg. 59718 (Sept. 23, 2020).
[3] 86 Fed. Reg. at 41384.
[4] 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).
[5] 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).
[6] *2020 Proposed Rule*, 85 Fed. Reg. at 59,719-20.
[7] *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.
[8] *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).
[9] 86 Fed. Reg. 41383, 41386.
[10] Id.
[11] Id. ("The House Report on the Medical Device Amendments of 1976 states that '[t]he Secretary may consider . . . use of a product in determining whether or not it is a device' (see H.R. Rep. 853, 94th Cong., 2d Sess. 14 (1976), reprinted in An Analytical Legislative History of the Medical Device Amendments of 1976, Appendix III (Daniel F. O'Keefe, Jr. and Robert A. Spiegel, eds. 1976)).").
[12] Id.
[13] Id. at 41390.
[14] Id. at 41388.
[15] Id.
[16] Id. at 41389.
[17] Id.
[18] Id.
[19] Id.
[20] Id. at 41390.
[21] Id.
[22] Id.
[23] Id. at 41390-41391.
[24] Id. at 41391.
[25] Id.
[26] Id.
[27] Id. at 41390-41395; *Central Hudson v. Public Service Commission*, 447 U.S. 557 (1980)
[28] 86 Fed. Reg. 41383, 41395.
[29] Id.
[30] Id.
[31] Id.
[32] Id. at 41395-41396.
[33] Id. at 41396.
[34] Id.
[35] Id.
[36] Id.; *see e.g.*, FDA, Draft Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices (February 2014), https://www.fda.gov/media/88031/download
[37] 86 Fed. Reg. 41383, 41396.
[38] Id.
[39] *See, e.g.*, FDA, Guidance for Industry, ''Medical Product Communications That Are Consistent With the FDA-Required Labeling—Questions and Answers,'' June 2018 (available at https://www.fda.gov/ media/102575/download); *see also* FDA, Guidance for Industry, ''IndustrySupported Scientific and Educational Activities,'' December 1997 (available at https://www.fda.gov/media/70844/ download); *see also* FDA, Draft Guidance for Industry, ''Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices,'' February 2014 (available at https://www.fda.gov/media/ 88031/download); *see also* FDA, Draft Guidance for Industry, ''Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices,'' December 2011 (available at https://www.fda.gov/ media/82660/download).
[40] 86 Fed. Reg. 41383, 41397
[41] Id. at 41396-41397.

[42] Id. at 41397.
[43] Id. at 41398.
[44] Id.
[45] Id.
[46] Id. at 41397.
[47] 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).