August 12, 2021

A Question of Intent: FDA Amends Intended Use Regulations with Goal to Provide More Clarity, but Significant Questions Remain

On August 2, 2021, FDA issued a final rule amending its drug and medical device regulations describing the types of evidence that FDA considers relevant to determining a product's "intended use." The concept of intended use is a cornerstone of FDA's regulatory scheme that determines whether and how the Agency regulates a product as a drug or device. This final rule represents the culmination of a nearly six-years-long rulemaking process that generated extensive comments from stakeholders. Most significantly, the final rule clarifies that a firm will not be regarded as intending an unapproved new, or off-label, use for a drug or device based solely on that firm's knowledge that the product was prescribed or used by health care providers for the use. More generally, FDA has made clear that it will continue to take a broad view of what evidence, including manufacturer communications and other information about the product, may be considered when determining intended use. The amended regulations also will expressly state for the first time that the "design or composition" of an article may be relevant to determining intended use.

In the preamble to the final rule, FDA states that the amended regulations are intended to "better reflect the Agency's current practices" and that it has no "reason to believe firms will change their marketing or operating procedures as a result of this rule."[1] Additionally, the preamble addresses the statutory and constitutional concerns raised by industry stakeholders to the proposed rule and to the existing intended use regulations more broadly, stating that "[o]ne of the purposes of this rulemaking is to put to rest any dispute about FDA's interpretation of its statute and regulations, and its policy . . . regarding evidence that may be relevant to establishing intended use."[2] Significant questions remain regarding how FDA will apply the amended intended use regulations in practice going forward and what other regulatory changes related to manufacturer communications (e.g., scientific exchange and other communications safe harbors) may be forthcoming.

Background of the Intended Use Rulemaking

FDA's intended use regulations—21 C.F.R. § 202.128 for drugs and § 801.4 for medical devices—were promulgated nearly seven decades ago and have long been controversial, particularly because of the inclusion of language in the regulations suggesting that a firm's knowledge of an off-label use may be sufficient to establish a new intended use. FDA has historically taken a broad view of intended use and has long looked to a wide range of sources, such as promotional claims, internal documents, and how products are distributed as evidence of intended use. Industry has argued that FDA's broad view of intended use raises constitutional issues and exceeds FDA's statutory authority. Causing further confusion for manufacturers, FDA and the Department of Justice ("DOJ") have at times made conflicting statements regarding the evidence that may be relied upon in determining intended use, including the relevance of a manufacturer's knowledge.

FDA published a proposed rule in 2015 to amend the regulatory definitions of intended use "to reflect how the Agency currently applies them to drugs and devices."[3] In January 2017, FDA then issued a final rule that adopted a new "totality of the evidence" standard for determining intended use.[4] In response, various industry groups raised concerns about the final rule and petitioned FDA to reconsider the amendments. FDA delayed the effective date of the final rule until March 2018 and then, in March 2018, delayed the effective date indefinitely.[5]

In September 2020, FDA published a new proposed rule that withdrew portions of the 2017 proposed rule that never became effective and purported to provide more clarity about the types of evidence relevant when FDA determines the intended use of a product.[6]

Summary of the New Final Rule

The new final rule amends the existing intended use regulations in two key respects. First, FDA has added language clarifying that a firm will not be regarded as intending an unapproved new use for an approved drug or legally marketed

device based "solely" on the firm's knowledge that the product is being prescribed or used by health care providers for the off-label use. Because off-label use of medical products is generally legal and in some cases may represent the standard of care, manufacturers have long argued that knowledge of off-label use should not trigger potential criminal liability. FDA and DOJ had previously stated in certain instances that a firm's mere knowledge of an off-label use would not establish a new intended use, but this policy had never been codified in the regulatory text. Second, FDA has added language stating that a firm's intent may be shown by the "design or composition" of an article. This new language is in addition to pre-existing regulatory text that permits FDA to consider a firm's "expressions" and the "circumstances surrounding the distribution of the article."[7]

The preamble to the final rule addresses comments from industry stakeholders that questioned FDA's interpretation of intended use on statutory, constitutional, and policy grounds.

Intended Use Based on Any Relevant Evidence. FDA explained that when determining a product's intended use, it can look to "any relevant evidence," including promotional claims as well as other evidence, such as circumstances surrounding the distribution of a product. Comments to the proposed rule argued that considering evidence other than promotional claims exceeded FDA's statutory and regulatory authority. FDA disagreed with these comments, arguing that nothing in the statute, the legislative history, or the existing regulation supports an approach to intended use that is exclusively based on promotional claims.

First Amendment Considerations. Industry stakeholders submitted comments to the proposed rule arguing that the proposed rule, and the intended use regulations more broadly, raised important First Amendment concerns and threatened to chill truthful, non-misleading manufacturer communications about unapproved uses. In response, the FDA argued that the final rule does not implicate the First Amendment because the particular changes to the codified language do not directly involve speech. The FDA added that a "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, including review of proposed labeling, and postmarket regulatory surveillance and actions."[8] FDA also reaffirmed the arguments from its 2017 memorandum addressing First Amendment issues, "Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products"[9] (see prior Ropes & Gray Alert). FDA emphasized the public health interests served by the Agency's current regulatory approach and asserted that various alternative approaches that have been proposed would be inadequate.

Fifth Amendment Considerations. Comments also argued that the rulemaking raises concerns under the Due Process Clause of the Fifth Amendment because the intended use regulations fail to provide sufficient clarity regarding the boundaries between permitted and prohibited communications. FDA disagreed with this argument, asserting that it is not required to regulate with "meticulous specificity." FDA noted that "courts have repeatedly rejected due process challenges to the [Federal Food, Drug, and Cosmetic Act] as unconstitutionally vague or ambiguous."[10] Additionally, FDA asserted that, in the almost 70 years since the intended use regulations were first issued, manufacturers have had "little difficulty" understanding how the FDA applies the regulation, despite extensive industry comments pointing to the lack of clarity in the regulatory scheme and the confusion caused by the intended use regulations.

Consideration of FDA Communications Safe Harbors, Including Scientific Exchange. Industry had requested that FDA make clear in the regulations that safe-harbored speech about off-label uses (e.g., scientific exchange, responses to unsolicited requests) would be excluded from an intended use inquiry. The Agency declined. The preamble merely states that the "final rule does not disturb any of FDA's acknowledged 'safe harbors,' including those that encompass various types of scientific exchange,"[11] and that knowledge in combination with "safe-harbored" speech would not be "determinative" of intended use. Although FDA appeared to acknowledge that some, but not all, scientific exchange will be excluded from the determination of intended use, it did not provide any clarity as to when safe-harbored speech, including but not limited to scientific exchange, would be regarded by the Agency as relevant to the intended use determination, and it rejected requests to codify the various safe harbors that appear only in non-binding guidance documents. FDA asserted that such requests were outside the scope of the rulemaking. The Agency acknowledged that it

has been engaged in a "continuing review" of regulations and policies regarding manufacturer communications, but did not provide any details of when its continuing review may be complete or what other actions may be part of it.

Implications for the Drug and Device Industries

FDA claims that the amended regulatory language regarding when a manufacturer's knowledge will establish a new intended use should reduce manufacturer uncertainty. There is reason to doubt that the amended regulations will provide such clarity, however. The amended regulations say that a new intended use will not be based "solely" on knowledge of an off-label use, yet FDA would still be free to consider a firm's knowledge of an off-label use in conjunction with other evidence of intended use, such as labeling, advertising, statements of company representatives, and other "circumstances surrounding distribution" of a product, which FDA has broadly interpreted in the past. As a practical matter, when evaluating whether a new, off-label intended use exists for a medical product, FDA would likely assert that other evidence besides knowledge helps to establish the new off-label intended use such that FDA would not be relying "solely" on a firm's knowledge.

Additionally, although FDA stated that it "welcomes and will continue to consider comments" related to manufacturer communications safe harbors and scientific exchange, FDA's refusal to address these matters through or at the same time as the intended use rulemaking leaves significant questions for industry regarding the scope and contours of these safe harbors.[12] FDA's vague reference to its "continuing review" of manufacturer communications rules and policies—which FDA initiated more than seven years ago in response to a citizen petition by the Medical Information Working Group to which Ropes & Gray serves as co-counsel (see prior Ropes & Gray Alert)—provides no details regarding what changes manufacturers might expect in the future.

FDA's statements in the preamble regarding the breadth of the intended use inquiry and the Agency's recommitment to its 2017 First Amendment memorandum could set the stage for a more aggressive approach to promotional enforcement. Manufacturers should continue to evaluate on a case-by-case basis promotional materials and other activities that FDA may consider to be "any relevant evidence" of intended use and should pay close attention to developments in FDA guidance documents for communications safe harbors.

FDA's intended use final rule will become effective September 1, 2021. If you have any questions regarding the final rule, please contact any member of our FDA regulatory practice or your usual Ropes & Gray advisor.

1. 86 Fed. Reg. 41,838, 41,384, 41,400 (Aug. 2, 2021).
2. *Id.* at 41,389.
3. 80 Fed. Reg. 57,756, 57,756 (Sept. 25, 2015).
4. 82 Fed. Reg. 2,193, 2,205-06 (Jan. 9, 2017).
5. 82 Fed. Reg. 14,319 (Mar. 20, 2017); 83 Fed. Reg. 11,639 (Mar. 16, 2018).
6. 85 Fed. Reg. 59,718 (Sept. 23, 2020).
7. 21 C.F.R §§ 201.128, 801.4 (2020).
8. 86 Fed. Reg. at 41,391.
9. 82 Fed. Reg. 6,367 (Jan. 19, 2017).
10. 86 Fed. Reg. at 41,395.
11. *Id.* at 41,396.
12. *Id.*