What To Know About FDA's 'Intended Use' Proposed Rule

By **Coleen Klasmeier** (October 8, 2020, 5:26 PM EDT)

On Sept. 23, the U.S. Food and Drug Administration published a new proposed rule amending Title 21 of the Code of Federal Regulations, Subsections 201.128 and 801.4 — the regulations defining "intended use."

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Although the proposed codified language removes the knowledge-only prong from the definition — a helpful development from the industry's perspective — it also adds a potentially limiting proviso and a new provision that would allow the FDA to regulate a product based on its "design or composition."

The proposal represents the latest development in a long-running proceeding in which the FDA has both recognized the importance of clarity in these critical provisions[1] and created confusion within industry regarding the scope of government's medical product jurisdiction and enforcement authorities.[2]

The 30-day deadline for comments, while appealing from the standpoint of quickly finalizing the rule, also presents a challenging calculus for stakeholders in the current political climate.

The Proposal

Intended use determines whether an article is properly regulated by the FDA as a drug or medical device and whether a new use has been created for which adequate directions are required in labeling under the misbranding provisions of the Federal Food, Drug and Cosmetic Act.

The scope of the intended use definition is of critical importance to drug and medical device developers as well as to consumer technology companies interested in assuring that their products remain outside the scope of the FDA's comprehensive regulatory authority.

Disputes over the scope of the intended use regulation date back to the provision's original promulgation and most recently have been the subject of industry petitions requesting targeted amendments. In September 2015, the FDA published a proposed rule in response to those petitions, but in 2017 controversy erupted with publication of the corresponding final rule, which took a different tack and was later stayed by the FDA in response to industry pressure.

Under this latest proposal, the intended use regulations would be amended in two key respects.

First, the FDA is proposing to delete the last sentence of each regulation and to add language "to clarify that a firm's knowledge that health care providers are prescribing or using its approved or cleared medical product for an unapproved use would not, by itself, automatically trigger" misbranding liability.

Second, the FDA is proposing to add a clause to the regulations to provide that intended use may be shown by not only promotional claims — "expressions," using the language of the regulations — but also by "the design or composition of the article."

The proposed rule is accompanied by the customary explanatory preamble, Section 3 of which sets

forth the FDA's analysis of the case law on intended use. As in prior rulemakings and other proceedings, here the FDA asserts a broad interpretation of intended use in which the agency is entitled to regard any source of evidence, subject only to a relevancy test. Of note, the even more capacious totality standard that was included in the 2017 final rule has been removed from the proposed codified text.

The FDA contends that "any claim or statement made by or on behalf of a firm that explicitly or implicitly promotes a product for a particular use may be taken into account" but then goes beyond this traditional, claims-based view. The FDA states that the claims-based approach would "create a loophole for firms that would enable them to evade FDA oversight" and "open the door to the marketing of products that are unapproved for any medical use."

As in the 2017 final rule preamble, the FDA explains that a more expansive interpretation of intended use is necessary to enable the agency to "pursue firms that attempt to evade FDA medical product regulation by avoiding making express claims about their products."

Section 5 of the preamble discusses two categories of intended use evidence. The first category involves evidence that the FDA asserts is relevant to intended use. The second includes "examples of evidence that, standing alone, are not determinative of intended use" — such as a manufacturer's mere knowledge of off-label use of a lawfully marketed drug or medical device.

Thus, the preamble explains, if a manufacturer collects product sales and distribution data and "notes that one of its products, approved for use only in adults, is being ordered by and distributed to many medical practices that treat exclusively pediatric populations," then the company's knowledge of the pediatric use would not be regarded as an intended use for which the manufacturer is accountable. [3]

Issues Raised by the Proposed Rule

The FDA's proposed rule in key respects grants the relief requested by industry in prior submissions. It strikes the final sentence from the regulatory definitions to address the practical and doctrinal problems presented by the knowledge prong and includes helpful preamble language responding to industry requests for affirmation that knowledge of off-label use combined with dissemination of information about new uses in accordance with applicable FDA guidance would not be treated as evidence of a new intended use.

In other respects, however, the proposed rule and the preamble present challenging issues, ranging from constitutional questions to questions of statutory authority. The proposal also presents practical challenges to manufacturers because of the continued lack of clarity provided by the FDA's approach.

First Amendment/Due Process

The FDA asserts that the rule, "if finalized, would be consistent with the First Amendment." The preamble explains that the rule "describes evidence that may be relevant" to intended use without dictating that any particular evidence "will be determinative ... in an individual case."

In an accompanying footnote, the FDA states that "[b]ecause 'intended use' is only one element of an alleged violation of the FD&C Act, this rule does not itself implicate the First Amendment and does not attempt to resolve all First Amendment arguments that might be made by a firm in defending against an enforcement action."

The FDA also addresses the First Amendment concerns presented by the proposed rule by pointing to various guidance documents that identify types of communications that ordinarily would not, on their own, establish intended use.

The preamble asserts, citing selected decisions from other contexts, that "[c]ourts have long upheld the premarket review requirements of the FD&C Act and the [Public Health Service] Act, and the role of intended use within that framework, as necessary to promote and protect the public health and as fully consistent with the First Amendment."

The preamble points to judicial decisions unfavorable to the FDA as well, but does so to distinguish or

otherwise neutralize them. The FDA does not explicitly acknowledge that developments in the past 10 years have called into question the validity of government restrictions, whether through application of the intended use doctrine or otherwise, on accurate off-label speech.

The preamble discusses examples of types of evidence that are relevant to establishing intended use in a way that raises due process concerns. For example, the preamble states that the examples "are provided for illustrative purposes only and are not intended to be comprehensive or restrictive."

Further, the FDA states that it "will evaluate the individual and unique circumstances of each case in determining a product's intended use." Likewise, in Section 5C, the FDA asserts that every scenario is fact-specific and that similar material to the communication that the FDA describes as permissible may be evaluated differently.

Whereas the traditional, claims-based interpretation of intended use enables manufacturers to determine the uses for which they are accountable under the FDCA, the FDA's broad approach — in which certain types of evidence are deemed "relevant" to "intended use" — challenges any firm's ability to self-determine compliance.

Because many of the relevant types of intended use evidence identified by the FDA comprise protected speech, the agency's approach raises both First and Fifth Amendment due process issues.[4]

Product Characteristics and Design

The FDA asserts that "[t]he characteristics of the product and its design are relevant to establishing intended use." The preamble identifies examples involving "known physiological effects" and known uses of consumer products as well as design or technical features of medical products.

Thus, the FDA asserts that it can regulate as a drug "coffee containing sildenafil," the active ingredient in approved drugs for erectile dysfunction and pulmonary arterial hypertension, presumably even in the absence of claims, instead of commencing enforcement action against such a product on the ground that it constitutes an illegal food product.

Similarly, the FDA asserts that it can regulate a lawfully marketed medical device according to uses for which the manufacturer has not sought marketing authorization and is making no claims if, in the FDA's view, the device has particular features — such as devices sized for unlabeled uses or with functions other than those for which they are marketed.

Circumstances Surrounding Distribution

In the past, industry has petitioned the FDA to remove the regulations' references to the circumstances surrounding distribution. The proposed rule would not affect those existing references.

In the preamble, the FDA reaffirms that such circumstances are among the types of evidence relevant to establishing intended use and provides additional commentary stating that, for example, "a firm's repeated proactive detailing and delivery of large amounts of complimentary product samples to a health care provider whose patient population does not fall within the product's approved population" is relevant intended use evidence.

The FDA cites, as a further example, the facts of U.S. v. Travia,[5] in which the FDA's circumstances theory of intended use in a case involving nitrous oxide sold at a music festival was at least arguably upheld by the U.S. District Court for the District of Columbia.

Scope of Safe Harbor

Of note, although the preamble describes the second category described above in terms of a safe harbor, the FDA makes clear that the examples in the second category are safe harbored only if they stand alone.[6] In other words, even the safe harbored conduct remains relevant to establishing intended use, and the safe harbor is effective only if the conduct is unaccompanied by other relevant evidence.

Similarly, in Section 5C, the FDA states that a manufacturer engaged in tracking product sales and distribution can have knowledge of an off-label pediatric use provided it "does not give any direction to its sales or marketing staff to disseminate samples or information about this product to these pediatric practices."

Section 5C of the preamble provides additional commentary that seemingly reflects the FDA's intention to be responsive to industry requests. The FDA states that "knowledge in combination with conduct that falls within an acknowledged FDA 'safe harbor' would not be determinative of intended use."

A manufacturer may, for example, distribute clinical practice guidelines pursuant to FDA guidance allowing dissemination of enduring materials relating to off-label uses, but again the preamble emphasizes that the government may use evidence of clinical practice guidelines distribution in an enforcement action if there is other intent evidence beyond knowledge of off-label use.[7]

Section 5C also identifies additional instances in which various types of evidence, standing alone, would not be determinative of intended use. A manufacturer may, for example, provide risk information about an off-label use to health care providers without that activity on its own establishing a new intended use.

In the accompanying example, of note, the off-label use is "broadly accepted by the medical community," the manufacturer "has submitted an efficacy supplement to add the unapproved use to the labeling," and the product is governed by a risk evaluation and mitigation strategy that provides for the manufacturer to "warn of potential risks related to the unapproved use in general terms."

In addition, the FDA states, in the example the manufacturer's risk communication "does not expressly or implicitly promote the efficacy of the unapproved use."

The other examples are similarly limited. In particular, the FDA states the following.

- A manufacturer can follow the social media account for a philanthropic rare disease patient organization in the circumstances outlined in the preamble, provided it "does not make any comments or otherwise endorse any specific posts."

- A manufacturer's CEO can present internal sales projections for an approved product at a meeting and can account for potential off-label sales — if the use is widely recognized as the standard of care and the meeting is internal.

- A manufacturer can make corporate filings or submissions to the U.S. Securities and Exchange Commission that describe development activities or include potential or actual off-label sales if these are required disclosures.

- Finally, a clinical trial sponsor can provide a plain-language summary of the trial's results to participants if the summary is provided solely "to acknowledge their contributions to scientific and medical advancement" and not to inform prescribing and use decisions and if the summary is factual, balanced and complete, includes relevant safety information and information about "any limitations of the study," does not make any conclusions about safety or effectiveness, and includes a conspicuous and prominent statement that the FDA has not authorized the product or use.[8]

Timing and Political Considerations

Comments on the proposed rule are due in 30 days unless the FDA grants an extension. Although many factors inform decisions regarding whether to seek an extension or submit comments and the

substance and tone of those comments, it is clear that a major driver here is electoral politics.

The FDA may take a more expansive view of its authority to interpret intended use in the presence of Democratic leadership, suggesting that industry should comment within the 30-day deadline and encourage the agency to finalize the proposed rule quickly, against the possibility of a change in administration.

Yet finalization seems unlikely even in the best case scenario because of the challenge of reviewing comments and preparing a final rule before the election and the difficulty of finalizing a significant rule between a general election and the inauguration.

Under the FDA regulations, the preamble accompanying the proposed rule has significant force as an expression of agency policy. Section 5C, which outlines instances in which a manufacturer may engage in various forms of expression without facing a significant risk of enforcement action, can therefore be regarded as currently binding on the FDA even in the absence of a final rule.

Likewise, however, the proposed codified and preamble language expanding the scope of intended use to include product characteristics and design reflects FDA policy. Comments to the FDA on the problematic aspects of the proposed rule could result in meaningful improvements in the final version.

Manufacturers will need to assess carefully the advantages and disadvantages of operating under the proposed rule versus a hypothesized improved final rule as they consider opportunities to submit comments to the FDA on this foundational doctrinal issue.

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[1] 85 Fed. Reg. 59718, 59720 (Sept. 23, 2020) ("FDA is proposing to repeal the portions of the final rule issued on January 9, 2017, that never became effective and to issue a new rule to provide more clarity regarding the types of evidence that are relevant in determining a product's intended uses. This action is intended to provide direction and clarity to regulated industry and other stakeholders").

[2] See, e.g., Citizen Petition from the Medical Information Working Group, FDA–2013–P–1079 (Sept. 3, 2013).

[3] Elsewhere in the preamble, FDA likewise explains that it would not regard a firm as "intending an unapproved use ... based solely on the firm's knowledge that such product was being prescribed or used by health care providers for such use." In an accompanying footnote, FDA states that "FDA generally does not seek to interfere with the exercise of the professional judgment of health care providers in prescribing or using, for unapproved uses for individual patients, most legally marketed medical products."

[4] FDA's interpretation of the intended use case law is also problematic, in its reliance on selected judicial decisions that appear to support a non-claims-based approach. See, e.g., Medical Information Working Group, Comments in Docket No. FDA-2015-N-2002, https://bit.ly/2FSwACQ.

[5] 80 F. Supp. 2d 115, 119 (D.D.C. 2001).

[6] In Section III of the preamble, e.g., FDA states: "FDA is clarifying in this rulemaking that while knowledge can be within the types of evidence that are relevant to establishing intended use, a firm's knowledge that its approved or cleared medical product is being prescribed or used by health care providers for an unapproved use would not be relied upon as the sole evidence of a new intended use."

[7] Similarly, in addressing First Amendment issues, FDA makes clear in a footnote that even those

types of communications that are consistent with recommendations in a guidance document may be regarded as evidence of a new intended use "if there is other evidence of a new intended use."

[8] FDA previously settled First Amendment litigation with a manufacturer on condition that the manufacturer be allowed to engage in this form of communication. Op. and Order at 55, Amarin Pharma, Inc. v. FDA, No. 15-3588 (S.D.N.Y. Aug. 7, 2015).
