FDA's Final Rule on Intended Use: 'Getting Right Back to Where We Started From'

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On August 2, 2021, the U.S. Food and Drug Administration (FDA) issued its final rule amending the intended use regulations codified at 21 CFR 801.4 and 21 CFR 201.128,[1] marking the end of an effort FDA began in 2015.[2] While the agency's 6-year rulemaking process took many turns along the way — and stakeholders tried repeatedly to limit the broad scope of the intended use regulations — in the end, FDA wound up "right back … where [it] started from,"[3] confirming that a manufacturer's "mere knowledge" of an unapproved use cannot, standing alone, constitute evidence of a new intended use, but FDA may consider such knowledge — along with a host of other factors — as evidence of intended use.

While the final rule provides greater insight into FDA's evaluation of intended use than did some of the interim iterations (most notably the 2017 Proposed Rule, which included a vague "totality of the evidence" standard), questions remain about how the agency will address various manufacturer activities that extend beyond "mere knowledge" but may be entitled to protection under the First Amendment. Ultimately, FDA continues to construe intended use broadly, and pharmaceutical companies and medical device manufacturers should continue to tread carefully when making any statements or claims that stray beyond FDA-approved labeling, even when those claims are truthful and non-misleading.

FDA's proposed changes to the intended use regulations merit attention because intended use shapes enforcement actions, criminal prosecutions, and False Claims Act (FCA) cases. FDA's labeling regulations define "intended use" as the objective intent of the persons legally responsible for the labeling of the drug or device — a definition that covers a broad array of activities and speech, which can then be used as evidence that a manufacturer is promoting its product beyond the indicated use.

Under this historical approach, FDA and the Department of Justice (DOJ) have cited a variety of "relevant sources" of evidence to establish intended use, including labels, labeling, advertisements, press releases, training documents, speeches and verbal statements — offered in a variety of contexts — to support enforcement actions based on the alleged sale of misbranded medical products. Industry has long argued that this approach overreaches and fails, among other things, to draw principled legal distinctions between promotional and non-promotional speech, a distinction FDA has rejected in the 2021 Final Rule.

A Brief Look Back

In 2015, FDA proposed eliminating a provision in the intended use regulations that required a manufacturer to provide adequate labeling if the manufacturer knew that its approved product was being promoted or used for an unapproved use.[4] This proposed revision eliminated the risk that the agency would bring an enforcement action based on a manufacturer's mere knowledge that its product was being used off-label. Drug and device makers received the 2015 proposed rule with hope that the proposal signaled an understanding by FDA of the challenges inherent in the existing intended use definition and that FDA would take the opportunity to amend the intended use rule to align more closely with various judicial defeats it had sustained under the First Amendment.

[1] *See* 86 Fed. Reg. 41,383 (Aug. 2, 2021) (2021 Final Rule).
[2] *See* 80 Fed. Reg. 57,756 (Sept. 25, 2015) (2015 Proposed Rule).
[3] Maxine Nightingale, "Right Back Where We Started From" (United Artists, 1976).
[4] *Id.*

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In 2017, however, FDA withdrew its proposed revision and proposed new language indicating that although the agency was eliminating knowledge evidence as the sole source of intended use, FDA would still look to the "totality of evidence" to determine intended use. FDA stated that both the 2015 proposed rule and the new proposal were intended "to clarify FDA's existing position on intended use, not to change it." Nevertheless, the "totality of evidence" standard sparked opposition from stakeholders who viewed it as introducing even more uncertainty to an already complex landscape and urged the agency to narrow or eliminate certain categories of intended use evidence.[5]

In September 2020, FDA withdrew the "totality of evidence" standard but declined to otherwise limit or exclude any of the types of intended use evidence on which the agency had traditionally relied. The agency clarified how it would treat a firm's knowledge of off-label uses by stating that "a firm would not be regarded as intending an unapproved new use … solely on that firm's knowledge that such [drug or device] was being prescribed or used by health care providers for such use."[6] However, tracking language that had long been in the relevant regulations, FDA reiterated that intended use may be established by circumstances in which the product is, with the firm's knowledge, offered or used for a purpose for which it is neither labeled nor advertised.[7]

The 2021 Final Rule

The 2021 Final Rule remains largely unchanged from the 2020 Proposed Rule. The only change in the codified language clarifies the regulation's applicability to devices that are exempt from premarket notification.[8] Nevertheless, a careful read of the 66-page preamble to the 2021 Final Rule reveals more of FDA's perspective. In the preamble, FDA has attempted to reconcile years of legislative history, decades of case law and numerous excerpts from agency briefs that underlie FDA's approach to intended use.

Although the long rulemaking odyssey may not have produced significant changes to the scope of intended use evidence, the 2021 Final Rule gives stakeholders a comprehensive repository of FDA's views on the issue. Whether the agency's approach will survive First Amendment scrutiny remains a pressing question, and the evolving jurisprudence seems certain to impact what enforcement actions FDA and DOJ will bring, even armed with such a permissive regulation.

So what evidence does FDA consider relevant to determining a medical product's intended use?

1. **FDA explains that evidence of intended use is not limited to promotional claims and derives from any relevant source.**

   A number of comments to the 2020 Proposed Rule encouraged FDA to focus primarily or exclusively on promotional claims. Others challenged FDA's authority to look to "any relevant source"[9] of evidence to determine intended use. Rejecting stakeholders' arguments that looking beyond promotional claims to consider a variety of other manufacturer activities and knowledge creates significant uncertainty — and potential First Amendment issues — the agency declined to take an exclusively claims-based approach. Instead, the agency referred to decades of case law and legislative history to assert its authority to rely on a broad scope of intended use evidence, stating that "intended use of a product may be determined from its label, accompanying labeling, promotional material, advertising, and any other relevant source."[10]

   Most importantly, FDA continues to assert that it is not limited to statements made by the manufacturer in determining intended use. Rather, the agency can establish intended use based on knowledge of actual use by customers, consumer conduct, the environment in which the product is sold, the absence of labeling, witness testimony, training programs, internal documents and financial arrangements, to name a few evidentiary sources. The FDA's confirmation that it may rely on a broad scope of evidence in evaluating intended use means that manufacturers will continue to face challenges in navigating the intended use regulations.

2. **FDA explains that design or composition of a medical product is relevant to intended use.**

   The codified language of the 2021 Final Rule defines intended use to include a medical product's "design or composition."[11] FDA states that the addition of "design or composition" to the meaning of intended use reflects long-standing and current policy that a product's characteristics may be indicative of intended use. For example, in FDA's view, a stent sized for a use different from the approved use is relevant to intended use, as is a spacer made to extract one liquid but designed with holes to extract a more viscous substance different from

[5] 82 Fed. Reg. 2,194 (Jan. 9, 2017).

[6] 85 Fed. Reg. 59,718, 59,720 (Sept. 23, 2020) (2020 Proposed Rule).

[7] *Id.* at 59,729.

[8] 2021 Final Rule at 41,384.

[9] *Id.* at 41,386.

[10] *Id.* (citing *United States v. Article of 216 Cartoned Bottles, "Sudden Change,"* 409 F.2d 734,739 (2d Cir. 1969)).

[11] *Id.* at 41,401.

the approved use.[12] Unlike the broad scope of considerations otherwise identified as potentially relevant to intended use, this criteria appears to be more objective and, because it does not involve speech, not as susceptible to First Amendment complications.

3. FDA explains that the intended use regulations do not implicate or violate the First Amendment.

In the 2021 Final Rule, FDA asserts that the intended use regulation does not implicate the First Amendment because intended use is only one element of a violation under the Federal Food, Drug, and Cosmetic Act (FDCA), and FDA is not seeking to regulate the speech itself. FDA notes that during premarket review and postmarket surveillance, the agency has always been required to review a firm's "speech" in the form of appropriate labeling and states that "[t]he categorical exclusion of all truthful speech from regulatory review would undermine FDA's ability to promote and protect the public health."[13] To support this position, FDA looks to case law involving other industries whose operations involve communications with the public and takes the view that "[i]t has never been deemed an abridgment of freedom of speech … to make a course of conduct illegal merely because the conduct was in part initiated, evidenced, or carried out by means of language, either spoken, written, or printed."[14]

While FDA has acknowledged stakeholders' concerns regarding the First Amendment implications of the 2021 Final Rule, including the interest of health care professionals and patients in information about off-label uses, the agency ultimately dismisses those concerns. FDA confirms that nothing in the 2021 Final Rule changes the agency's policies and practices as set forth in guidance documents relating to circumstances in which FDA does not intend to object to a firm's product communications or to view such communications as evidence of a new intended use. In doing so, it rejects the argument that recent First Amendment case law prohibits the 2021 Final Rule as a content-based restriction on free speech.[15] And FDA asserts that it can — consistent with the First Amendment — prove misbranding by using "promotional speech" as evidence that a medical product is intended for a use that falls outside its FDA-approved label.

While FDA acknowledged stakeholders' First Amendment concerns, it is not clear that FDA appreciates the complexity created by the intended use regulations. Under the Supreme Court's ruling in *Central Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n of New York*, commercial speech cannot be restricted unless: (i) the restriction is justified by a substantial government interest, and (ii) the means used to directly advance the government interest is not more extensive than necessary to serve the interest.[16] The Supreme Court has recognized that the First Amendment is particularly important "in the fields of medicine and public health, where information can save lives."[17] FDA views its public health mandate as justifying restrictions on speech inherent in the intended use regulations.

Given the breadth of factors involving speech that FDA addresses in the preamble to the 2021 Final Rule — such as training programs and internal documents, for example, whether FDA's approach is "not more extensive than necessary" to serve its public health goals is unclear. Coupled with the agency's insistence that it can pursue civil and criminal misbranding cases based, at least in part, on such activities, the application of the intended use regulation will likely continue to engender First Amendment challenges.

4. FDA explains that the 2021 Final Rule does not violate the Fifth Amendment as impermissibly vague.

The preamble to the 2021 Final Rule similarly dismisses criticisms that the intended use regulations are unconstitutionally vague, with FDA relying on a litany of cases holding that use of an intent standard does not render a statute unconstitutionally vague, even in a statute regulating speech.[18] FDA points out that courts have routinely rejected due process challenges to FDA's authority under the FDCA as unconstitutionally vague or ambiguous, and asserts that "[o]ver nearly seven decades, medical product manufacturers have shown little difficulty in understanding how the [intended use] regulations are applied."[19] FDA's view that the intended use regulations are clear may not relieve the concerns of manufacturers who continue to question how the agency will perceive various key product support activities, such as providing safety information regarding off-label uses.

[12] *Id.* at 41,390.

[13] *Id.* at 41,391.

[14] *Id.* at 41,392, referencing *Rumsfeld v. Forum for Academic and Institutional Rights, Inc.*, 547 U.S. 47, 62 (2006).

[15] *Id.* at 41,394-395.

[16] 447 U.S. 557, 566 (1979).

[17] *See Sorrell v. IMS Health*, 564 U.S. 552, 566 (2011).

[18] *Id.*

[19] *Id.*

FDA's Final Rule on Intended Use: 'Getting Right Back to Where We Started From'

5. FDA explains that the 2021 Final Rule will not change its current "safe harbors" for certain medical product communications.

In its preamble to the new rule, the agency reiterated that the 2021 Final Rule "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."[20] FDA noted that this includes policies and practices articulated in various guidance documents, including FDA's June 2018 Guidance for Industry, "Medical Product Communications That Are Consistent With the FDA-Required Labeling — Questions and Answers."

However, FDA did not expressly exclude "safe harbor" communications, such as scientific exchange and communications with health care providers about unapproved uses, as evidence of intended use. Instead, the agency expressed interest in continuing discussion around formalizing "safe harbor communications," but stated that codifying such safe harbors was beyond the scope of this rulemaking. While such certainty would be reassuring, given FDA's statement that its policies and practices have not changed, its unwillingness to codify the safe harbors at this point should not create additional uncertainty as to their application.

6. The 2021 Final Rule offers helpful fact scenarios to illustrate the kinds of evidence that, standing alone, would not determine intended use.

Perhaps of most value in the record of the new intended use rule are the examples provided to illustrate facts that, standing alone, the agency would not consider as evidence of a new intended use. Although FDA notes that every situation will be evaluated on its own unique facts, the illustrations offer stakeholders insight in assessing the level of risk in their own conduct and operations.

a. A firm will not be regarded as intending an unapproved use of an approved product based solely on that firm's knowledge of such use.

"A pharmaceutical firm tracks sales and distribution metrics. The firm 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. **The firm does not give any direction to its sales or marketing staff to disseminate samples or information about this product to these pediatric practices."**[21]

b. Knowledge combined with conduct that falls within an acknowledged "safe harbor" would not be determinative of intended use.

"A pharmaceutical firm tracks sales and distribution metrics. The firm notes that one of its products, approved for the treatment of adult patients with acute lymphoblastic leukemia (ALL), is being ordered by and distributed to many medical practices that treat exclusively pediatric oncology populations. The firm also notes that the National Comprehensive Cancer Network clinical practice guidelines (CPG) for the treatment of ALL in pediatric patients recommends the firm's drug product as a treatment option. The pharmaceutical firm distributes copies of the CPG at medical conferences, following all recommendations made in the revised draft guidance, 'Distributing Scientific and Medical Publications on Unapproved New Uses — Recommended Practices.'… **The firm does not give any direction to its sales or marketing staff to disseminate samples or information about this product to practices that treat pediatric cancer patients exclusively."**[22]

c. In certain circumstances, a firm's dissemination of safety information about an unapproved use to health care providers to minimize risk to patients would not be dispositive of a new intended use.

"The 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 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 health care providers 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."**[23]

FDA also provided the following examples of fact patterns that firms may routinely encounter in the normal course of their business that would not trigger regulatory action.

- **Social Media**

"A firm's official social media account "follows" the social media account for a 501(c)(3) nonprofit 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

[20] *Id.* at 41,396.

[21] 2020 Proposed Rule at 59,725, incorporated by reference into the 2021 Final Rule.

[22] *Id.*

[23] *Id.* at 59,725-726.

its FDA-approved products for use in the rare disease that the nonprofit account supports. The nonprofit account disseminates messages about charity events, scientific conferences, support groups, and rare disease research and drug development. **The firm account does not make any comments or otherwise endorse any specific posts on the nonprofit account.**"[24]

- **Sales Projections**

  "During an internal 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."[25]

- **SEC Filings**

  "A firm makes corporate filings or submissions to the U.S. Securities and Exchange Commission that include required disclosures of development activities or potential or actual sales for an unapproved use."[26]

- **Clinical Trial Preliminary Results**

  "Following a clinical trial, the sponsoring firm prepares a plain-language summary of the aggregated clinical trial results and provides the summary solely to clinical 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 any limitations of the study. **The summary does not make any conclusions about the safety or effectiveness of the unapproved product or the unapproved use, and it includes a conspicuous and prominent statement that the product or use has not been approved, cleared, or licensed by FDA.**"[27]

Conclusion

Over the course of FDA's 6-year rulemaking process, the agency has made clear that knowledge of off-label use, standing alone, will not be sufficient evidence of intended use, absent circumstances showing objective intent by the firm to otherwise promote the unapproved use. FDA's effort to provide specific examples of how it intends to treat certain commonly occurring scenarios is helpful, both because statements in preambles to rulemakings are legally binding and because the examples seem to point to a larger message: Where the facts do not suggest affirmative conduct by a company to cause an off-label use unsupported by scientific consensus, FDA will be less likely to consider the conduct as evidence of intended use requiring adequate labeling.

Those hoping the 2021 Final Rule would dramatically limit FDA's legal options regarding intended use may be disappointed, but they should not be surprised. FDA continues to assert the obligation — and need — to look broadly to any relevant source of evidence to establish intended use. The agency believes it can do so without differentiating between promotional and non-promotional speech and without implicating the First Amendment.

In the final analysis, the 2021 Final Rule essentially repurposes FDA's old playbook. The critical question now is what will FDA do under the breadth of this rule: What types of misbranding cases will it initiate — and which will it avoid — as First Amendment cases against the agency continue to raise enduring questions about the government's regulatory relationship to truthful, non-misleading speech?

[24] *Id.* at 59,726.
[25] *Id.*
[26] *Id.*
[27] *Id.*

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