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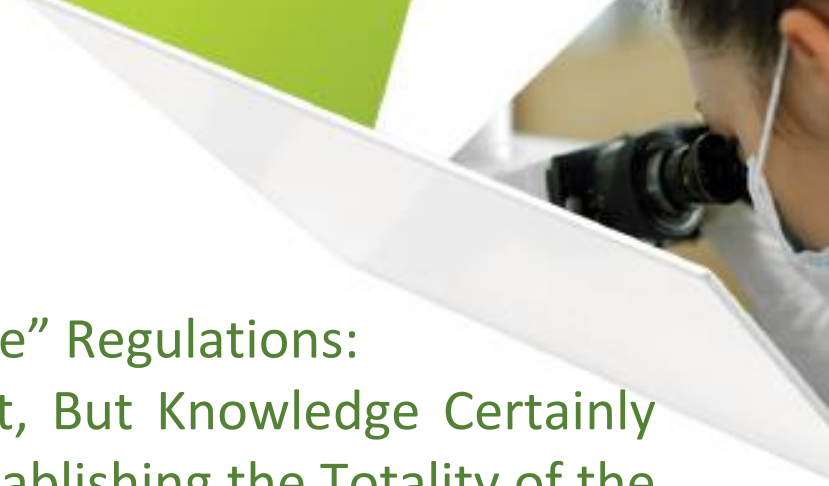

FDA Clarifies "Intended Use" Regulations: Knowledge Alone ≠ Intent, But Knowledge Certainly Can Be One Element in Establishing the Totality of the Evidence

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In its January 9, 2017 final rule addressing when tobacco products may be regulated as drugs, devices, or combination products, the Food and Drug Administration (FDA) amended the intended use regulations for drugs and devices. Importantly, though, the amended language is meant to provide clarity for drug and device manufacturers generally regarding FDA's interpretation and application of its existing definitions of "intended use," not to change them. Specifically, the final rule amends the last sentence of 21 C.F.R. § 801.4 (for devices) and 21 C.F.R. § 201.128 (for drugs) to clarify that a manufacturer's knowledge, alone, that its product is prescribed or used by physicians for an uncleared/unapproved use is not proof *in and of itself* that the manufacturer intends such use, nor is it sufficient to trigger the obligation to provide adequate labeling for that unapproved use. The amended language clarifies that a new intended use is created, and a manufacturer is required to provide adequate labeling on such use, only if the *totality of the evidence* shows that the manufacturer objectively intends for a drug/device to be used for uncleared/unapproved conditions or purposes.

The intended use language of the final rule, while different than what was initially presented in the proposed rule (see our prior comments on the proposed rule here), is consistent with the intent of the proposed rule, which was published on September 25, 2015.[1] FDA originally sought to clarify the role of manufacturer knowledge in determinations of intended use by altogether deleting the final sentence of the drug/device intended use regulations, which currently states:

> "But if a manufacturer knows, or has knowledge of facts that would give him notice that a device [or 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 device which accords with such other uses to which the article is to be put."

However, FDA concluded based on comments on the proposed rule that this approach might lead to further confusion, as some commenters suggested that FDA was renouncing its ability to consider knowledge of unapproved uses as part of an intended use determination at all. In order to avoid this confusion and preserve the ability to rely on knowledge of unapproved uses as part of the totality of evidence of intended use, FDA has chosen to amend this last sentence rather than delete it. The amended regulations now specify that objective intent may be shown by, among other things,

[1] *Clarification of When Products Made or Derived from Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses"* (Final Rule, 82 Fed. Reg. 2193; Proposed Rule, 80 Fed. Reg. 57756).

circumstances in which the manufacturer knows of a product's use for a purpose for which it is not labeled or advertised, to make it abundantly clear that manufacturer knowledge may be one source of evidence of intended use, but cannot be the sole source of evidence. FDA's position under the now-amended definition of intended use is consistent with how the Agency has historically interpreted these regulations. Interestingly, FDA made a point of clarifying that the changes to the intended use regulations are limited to legally marketed products, and do not apply to products that are not legally marketed as medical products for at least one use. This position seems to be consistent with recent enforcement activity regarding alleged preapproval claims about investigational drug products.

Not surprisingly, with the recent spate of First Amendment challenges to FDA's attempts to restrict drug and device manufacturers' speech regarding unapproved uses of approved products, the proposed rule triggered a number of stakeholder comments regarding the extent to which the First Amendment allows manufacturers to share truthful, non-misleading information about unapproved uses of their approved products. With the Agency's assessment of these broader policy questions ongoing, FDA largely sought to table these issues for another forum, but did take the opportunity to recite considerable jurisprudence to emphasize that courts have long held FDA may constitutionally rely on manufacturer speech as evidence of intended use under the Federal Food, Drug, and Cosmetic Act.[2] In response to comments that the First Amendment prohibits considering knowledge as evidence of intended use, the Agency articulated its position that speech is not the only display of a person's knowledge; thus, maintaining knowledge as one factor in determining intended use is not at odds with the protection of free speech. Finally, FDA also maintained its position that evidence relevant to intended use should include manufacturers' statements in various contexts, refusing to narrow the scope of evidence for this determination to solely statements in product labeling and some promotional material. In short, the Agency took the opportunity afforded by these pointed comments to restate its position on these issues generally, and these positions do not appear to have shifted since the recent First Amendment challenges and settlements or the Agency's November 9-10, 2016 public hearing.

Ultimately, the proposed (and now final) rule's revision of the drug/device intended use regulations does little to change long-standing FDA policy. Still, given the significant role played by the concept of intended use in driving FDA's jurisdiction over medical products, the codification of this interpretation is a notable development. Overall, the amended language of the final rule, if not ultimately rescinded by Congress under the Midnight Rules Relief Act[3], can be counted as a "win" for industry, as it explicitly eliminates the possibility (however remote) of FDA enforcement action based solely on a manufacturer's knowledge of an off-label use of its product.

[2] This is largely based on Supreme Court precedent establishing that "[t]he First Amendment … does not prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent" (*Wisconsin v. Mitchell*, 508 U.S. 476, 489 (1993)).

[3] Although the final rule is set to become effective 30 days after publication (on February 8, 2017), it is subject to the risk of rescission by Congress under the Midnight Rules Relief Act (which was recently passed by the House) before it even takes effect. Should the Midnight Rules Relief Act pass the Senate and be signed into law by incoming President Trump, the bill would amend the Congressional Review Act (CRA) to allow Congress to group multiple new regulations together and disapprove them all at once. Should this happen, reversion to the existing intended use language would not be expected to have any practical significance, given FDA's historical interpretation of the intended use regulations.

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