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FDA Proposes to Indefinitely Delay Obama Administration Amendments to FDA Regulations on Intended Use

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In an announcement that has implications for the debate over off-label promotion, FDA is proposing to delay, until further notice, the effective date of portions of a final rule amending its regulations that describe the types of evidence that the agency may consider in determining the "intended use" of a drug or medical device.

This new language on intended use was included in an otherwise largely non-controversial final rule, published on January 9, 2017, during the closing days of the Obama Administration, which primarily addressed when tobacco products will be regulated as drugs, devices, or combination products.

FDA explained that it is proposing to indefinitely delay the effective date of the amendments to the drug and device intended use regulations "to allow further consideration of the substantive issues raised in the comments received." FDA must solicit public comment on this proposed delay (comments are due by February 5, 2018), consider the comments submitted, and prepare and publish a final notification of the delay before March 19, 2018, when the final rule is scheduled to take effect. FDA's proposal is clearly good news for the drug and device industries, which raised concerns that the new "totality of the evidence standard" would create confusion and give regulators too much subjectivity when determining "intended use." This proposal (if finalized) does not, however, resolve the debate over off-label promotion, and companies should continue to exercise caution until FDA issues substantive guidance on this issue.

Background and Analysis

"Intended Use" is a fundamental concept in the Federal Food, Drug, and Cosmetic Act, FDA regulations, and food and drug case law. Intended use determines *whether* a product is regulated as a drug or device and has significant implications for how drug and device manufacturers communicate about and promote their products. Evidence that a firm intends its approved product for unapproved uses (often referred to as off-label promotion) can result in substantial criminal and civil penalties.

The January 9, 2017, 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 FR 2193) made two changes to existing FDA regulations regarding "intended use" (21 CFR 201.128 for drugs and 21 CFR 801.4 for devices).

First, the last sentence of the regulations previously stated that if a manufacturer knows or has notice that its approved drug or device is used for unapproved uses, the manufacturer must provide adequate labeling for that use. This sentence was deleted by the amendments. Although the sentence had been in the regulations for a long time, it had *not* been FDA's policy to enforce it. Were FDA to enforce this provision, whenever a manufacturer knew its drug or device was prescribed or used off-label, the manufacturer would be required to include directions for that use in the product's labeling, and the labeling would need to be FDA-approved. In the rulemaking, FDA stated that, absent extraordinary circumstances, the agency will not regard a firm as intending an unapproved use based *solely* on the firm's knowledge that a product is prescribed or used off-label. Industry had expressed concerns about this "manufacturer's knowledge" provision for many years, and FDA responded by making the regulation consistent with agency policy.

The second change to the regulations, however, was more controversial. FDA added a new last sentence to the final rule that was not in the original proposed rule, stating that if the *totality of the evidence* establishes that a manufacturer intends a drug or device to be used for an unapproved use, the manufacturer is required to provide labeling for that use. FDA stated that it was codifying the agency's longstanding position that in determining a product's intended use, FDA may look to any relevant source of evidence.

The life sciences industry was concerned, however, that the "totality of the evidence" language expanded the types of evidence that could be considered in determining intended use. Several comments, and a Citizen Petition filed by several industry organizations asking FDA to reconsider and indefinitely stay the final rule, raised legal concerns with the final rule, including arguments that:

1. Truthful and non-misleading speech cannot be the basis of a manufacturer's intended use under the First Amendment, citing to the *Caronia* and *Amarin* cases.
2. The final rule violates the Due Process Clause of the Fifth Amendment because the types of evidence to be considered are not clearly defined.
3. The final rule unlawfully interferes with the practice of medicine.
4. The final rule departs from statutory text, legislative history, case law, and FDA past practices, and
5. FDA did not give stakeholders an opportunity to comment in violation of the Administrative Procedure Act because the "totality of the evidence" language was not in the proposed rule.

In addition to these legal concerns, several comments asserted that the final rule could have potentially negative health implications. The "totality of the evidence" standard would permit FDA to rely on non-promotional scientific exchange (*e.g.*, company responses to unsolicited requests for information about unapproved uses, sponsorship of continuing medical education and other scientific or educational activities, dissemination of medical journals and scientific or medical reference publications) as evidence of intended use, thus chilling important communications between manufacturers and patients, healthcare professionals, and payors.

Because the final rule was published in the final days of the Obama administration, it was subject to a regulatory freeze enacted by the Trump administration. Accordingly, FDA delayed the effective date of the rule until March 21, 2017, and further delayed the effective date until March 19, 2018 (and invited public comment), in order to consider the Citizen Petition and public comments.

In announcing the proposal to indefinitely delay the effective date of the intended use amendments in the final rule, FDA Commissioner Scott Gottlieb, M.D., stated that, "We need more time to consider the feedback we received and to make sure that our approach is guided by our public health mandate and to ensure the clarity of our rules on the subject."

Conclusion

FDA's proposal to delay, until further notice, the effective date of the intended use amendments in the January 9, 2017, final rule is not surprising. The final rule was issued in the final days of the Obama administration (along with two draft guidances on manufacturer communications and a memorandum analyzing First Amendment considerations) and the "totality of the evidence" language can easily be read to expand the types of evidence FDA could consider in determining intended use, thus limiting what drug and device manufacturers can say about unapproved uses. Moreover, in writings and speeches before becoming FDA Commissioner, Dr. Gottlieb has been critical of FDA's restrictions on off-label communications.

It is a little surprising that FDA chose to indefinitely delay the rule's implementation rather than to revoke or revise it and to not delay the non-controversial deletion of the "manufacturer's knowledge" sentence. FDA clearly has the authority to stay "for an indefinite time period" the effective date of an action or decision on any matter (*See* 21 CFR 10.35[a] and [b]). Moreover, given the number of high-priority issues on FDA's plate (*e.g.*, drug pricing/increasing generic competition, Opioids, implementing 21st Century Cures provisions), it is understandable that the agency needs more time to consider the issues surrounding intended use. Although the proposed delay of the "totality of the evidence" standard is good news for industry, the downside to the indefinite delay is the loss of the benefit of the codification that knowledge alone could not be the basis for intended use. Industry will have to rely on current and past FDA statements that the agency will not find intended use based on knowledge alone.

FDA's proposal is clearly an encouraging sign to the drug and device industries that the agency has heard their concerns about intended use and product communications. Companies would be prudent, however, to continue to exercise caution regarding promotional activities discussing unapproved uses until such time as FDA issues substantive guidance on this issue.
