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The FDA's "Intended Use" Regulations Should Not Restrict Actions to Meet Market Demand for Off-Label Use

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In September 2021, the Food and Drug Administration's newly amended "intended use" regulations took effect. *See* 21 C.F.R. §§ 201.128 (drugs), 801.4 (devices) (as amended). The regulations describe the types of evidence that the Agency will consider in evaluating whether a company marketed a drug or medical device for a use not approved by the FDA. An unapproved use is often referred to as a "new" or "off-label" use.

When the FDA approves a drug or device, it approves the product for one or more specific uses, which are included in the product's FDA-approved labeling. Healthcare providers may and commonly do prescribe drugs and devices for off-label use,[1] and off-label use may in some circumstances become the prevailing standard of care for physicians. However, the Food, Drug, and Cosmetic Act ("FDCA") generally prohibits manufacturers from selling drugs or devices without approved labeling for all intended uses because such products are considered "misbranded" or "adulterated." *See, e.g.*, 21 U.S.C. §§ 331(a), 351(f), 352(a) & (f).

The 2021 intended use amendments clarified that a company's knowledge that its product is being prescribed or used off-label is insufficient on its own to establish the intended use element of an FDCA violation: "[A] firm would not be regarded as intending an unapproved new use … based solely on that firm's knowledge that such [product] was being prescribed or used by health care providers for such use." 21 C.F.R. §§ 201.128, 801.4. The FDA may, however, consider a company's knowledge of off-label use along with other evidence or circumstances to determine whether a company intended for a product to be used off-label. In making an intended use determination, the FDA may look, for example, at a company's express and implied promotional claims, the product's characteristics and design, and the circumstances of the product's manufacture, distribution, or sale. *See* 21 C.F.R. §§ 201.128, 801.4; Regulations Regarding "Intended Uses," Final Rule, 86 Fed. Reg. 41,383, n.3 (Aug. 2, 2021) (to be codified at 21 C.F.R. §§ 201.128, 801.4) ("Final Rule").

The amended intended use regulations have prompted many questions from industry, including whether the Agency could find that a company violated the FDCA by manufacturing more of a drug or device than it would need to meet the anticipated demand for on-label prescriptions because it was aware of off-label use. So far, neither the FDA nor the courts appear to have directly addressed this question. As discussed below, however, the intended use regulations, FDA statements, and case law suggest that a drug or device manufacturer's consideration of off-label use in determining how much of a product to manufacture, including a decision to increase its production level based on knowledge of off-label use, should not, on its own, establish intended use.

First, under the regulations, any inquiry by the FDA into whether a company intended for its product to be used off-label must look beyond mere knowledge or awareness of off-label use to determine the company's "objective intent" with respect to the labeling of its product. 21 C.F.R. §§ 201.128, 801.4. The FDA's comments on the regulations suggest that information that a company obtains about market demand for off-label use of a product, including sales and distribution data, is the type of knowledge that is insufficient on its own to be determinative of intended use. *See* Regulations Regarding "Intended Uses," Proposed Rule, 85 Fed. Reg. 59,718,

[1] The federal Agency for Healthcare Research and Quality reports that off-label prescribing "is legal and common," with "one in five prescriptions written … for off-label use." Agency for Healthcare Research and Quality, Off-Label Drugs: What You Need to Know (Sept. 2015).

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59,726 (Sept. 23, 2020) ("Proposed Rule"). The FDA has explained, for example, that it would not make an intended use finding based on a company's knowledge from "track[ing] sales and distribution metrics" that a product "is being ordered by and distributed to many medical practices that treat exclusively" a patient population for whom the product is not approved. *Id.* at 59,725.

Similarly, the FDA has confirmed that neither of the following scenarios would support a finding that a company improperly marketed an unapproved use:

- "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."
- "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."

Id. at 59,726.

These examples show that the FDA understands that companies can and should be able to evaluate and account for product sales for unapproved uses both through backward-looking analyses and forward-looking planning activities. They also suggest that a company's decision to increase manufacturing output beyond the anticipated demand for on-label use based on projected demand for off-label use should not, without more, establish an intended use.

Second, based on FDA comments on the amended intended use regulations, as well as court cases applying earlier versions of the regulations, merely manufacturing product to meet a demand for off-label use should not trigger an intended use finding. Instead, the FDA and courts look for evidence of affirmative conduct by the company to "*create[] a market*" for off-label use. *United States v. 789 Cases, More or Less, of Latex Surgeons' Gloves*, 799 F. Supp. 1275, 1285 (D. P.R. 1992) (emphasis added). In addition to making explicit promotional claims about off-label use, such affirmative conduct may include:

- Providing samples of a product to a healthcare provider whose patient population does not fall within the product's approved population. Proposed Rule, 85 Fed. Reg. at 59,725.
- Training healthcare providers on a product's unapproved use. *See United States v. An Article of Device . . . "Toftness Radiation Detector,"* 731 F.2d 1253, 1255 (7th Cir. 1984).
- Selling to a *single* customer with knowledge that the customer's use for the product is unapproved. *789 Cases, More or Less, of Latex Surgeons' Gloves*, 799 F. Supp. at 1295.

In these examples, to establish the intended use element of an FDCA violation, the government looked to specific actions or statements by the company that were directed to actual or potential customers and that showed that the company intended that its product would be used off-label. By contrast, a company's decision to manufacture a product at a level that accounts for the possibility that some amount of the product will be used off-label by some customers does not, on its own, involve an affirmative act to promote or cause off-label use.

Finally, the FDA's lack of historical enforcement activity against companies for accounting for off-label use in setting drug or device production levels, and its repeated observation throughout the Final Rule that the recent amendments to the intended use regulations "do not reflect a change in the FDA's policies and practices," further suggest that this is not the type of business activity that the Agency intends to regulate through these rules.[2] Final Rule, 86 Fed. Reg. at 41,390; *see also id.* at 41,396 ("This 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."); *id.* at 41,399. The FDA also acknowledges in the Final Rule that healthcare providers may prescribe products for unapproved uses and that manufacturers are not required to confirm a healthcare provider's planned use for a product before distributing it. *See id.* at 41,398 & n.4. These acknowledgments further support an understanding that companies should be able to consider market demand for a product for off-label use in deciding how much product to manufacture without the fear of FDA enforcement activity based on the intended use regulations.

[2] Other than certain controlled substances and drug chemicals that are subject to production quotas set and enforced by the DEA pursuant to a separate statutory regime, drugs and devices approved by the FDA are generally not subject to production limits.

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