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Off-Label Uses

The Vexing Problem of Defining Intended Use: A Proposed Solution

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On January 12, the FDA announced a further one-year extension of the effective date of its 2017 rulemaking that defined the ''intended use'' of an article for purposes of establishing whether that article was a ''drug or device'' for FDA regulatory purposes. The controversial 2017 rulemaking defined ''intended use'' as established by a seller's ''objective intent'' based on the ''totality of circumstances'' relating to how its product was marketed and used. Opponents justifiably contended that this definition was hopelessly vague, potentially overbroad and, to the extent it permitted the dissemination of truthful and non-misleading scientific information about the use of a drug or device to establish ''intended use,'' a violation of the First Amendment. This article proposes a means of resolving this dispute that would safeguard the legitimate interests of both sides.

FDA's adoption of a vague ''intended use'' definition as the benchmark for subjecting sellers to FDA's drug/device authority could be viewed as an effort to gain expanded, and essentially unreviewable, power over the scope of FDA jurisdiction. The problem is especially sensitive in medical device regulation where intended use can determine regulatory product classification and the burden involved in demonstrating safety and effectiveness. But, in defense of FDA, it has a legitimate public health interest in ensuring that patients using drugs and devices are protected against false or unproven claims and it is far from clear that any other definition of ''intended use'' would resolve the underlying jurisdictional issue to the satisfaction of the potentially regulated seller community and those looking to the FDA to protect public health.

Conceptually, a major inherent difficulty in defining ''intended use'' is that FDA regulates the conduct of manufacturer/sellers but has no regulatory control of consumer/users. The ''use'' the seller intends for its product may differ from the uses the buyer intends to make of it. Take, for example, an amulet intended and promoted by its seller as an attractive piece of jewelry but believed by a number of buyers to have valuable therapeutic properties. Looking at ''intended use'' from the seller's perspective, there is no basis for subjecting the seller to drug/device regulatory requirements not applicable to jewelry manufacturers. From the buyer's perspective, however, there is good reason to afford the regulatory safeguards applicable to the side of alternative therapies. To avoid this choice of perspective in the absence of legislative direction, FDA invented the vague term ''objective intent'' that seemed peculiarly to attribute intent to the article itself. FDA then compounded that vagueness with its ''totality of circumstances'' rule.

FDA sought to exploit the vagueness of ''intended use'' when it sought to regulate tobacco products whose manufacturers made no therapeutic claims—and indeed by law warned that their products were unhealthy. FDA found that tobacco consumers intended to benefit from the chemical effects of the nicotine delivered by tobacco products and that manufacturers knowingly designed their products to deliver nicotine dosage. Thus, FDA concluded that tobacco manufacturers/sellers ''objectively'' had the intent to market products containing the drug nicotine to affect the structure or function of the human body and could be subjected to drug and device regulation. Tobacco manufacturers argued, to the contrary, that the absence of any claim of health benefit on their part foreclosed FDA regulation.

It was anticipated that the Supreme Court would clarify the scope of ''intended use'' when it granted review of the tobacco manufacturers challenge to FDA's tobacco regulations in *FDA v. Brown & Williamson*. The Court, however, side-stepped the issue by striking down FDA's regulations on the separate ground that Congress had made clear its intent to exempt tobacco products as customarily marketed from FDA regulation. Congress then responded by enacting a separate FDA

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regulatory regime for tobacco products leaving open only the ancillary question whether health benefit claims by tobacco product manufacturers like e-cigarette makers could subject their products to more stringent drug/device regulations. It was in the course of resolving this question that FDA adopted its ''totality of circumstances'' standard for asserting drug/device marketing controls.

The ''totality of circumstances'' definition drew strenuous opposition from drug and device manufacturers who rightly feared that it could give FDA expanded power to hold them accountable for ''off-label'' use of their approved products. Simply put, ''off-label'' use occurs when a drug or device lawfully marketed as safe and effective for specified purposes in specified patient populations is used by doctors and patients to treat other conditions or other patient groups. Manufacturer/sellers found to be marketing their products for ''off-label'' use can be and have been charged with unlawfully ''misbranding'' their products by failing to provide adequate instructions for those uses as well as with the unauthorized distribution of an unapproved new drug or device. In addition, federal insurance programs like Medicaid generally do not cover the cost of ''off-label'' uses. But prescribers of drugs/devices are not required to specify why a prescription is written allowing off-label prescriptions to be routinely filled. The federal government thus can claim a financial loss when it pays for ''off-label'' prescriptions presented by covered patients. If a manufacturer/seller can be found to have ''intended'' off-label use, it can be charged with knowingly ''inducing'' unlawful ''off-label'' insurance claims making it liable for treble damages under the False Claims Act. Federal recovery of tens of billions of dollars has been generated by this inducement theory.

FDA has never taken the position that ''off-label'' use by itself, whether or not the manufacturer/seller is aware of it, is attributable to the manufacturer/seller as ''intended use.'' Rather, FDA seeks to focus on some aspect of manufacturer/seller conduct that can be said to have promoted ''off-label'' use. Because express manufacturer/seller promotion of ''off-label usage is relatively rare, FDA often focuses on manufacturer/seller dissemination of third-party scientific information relating to off-label uses without express advocacy as well as focusing on quantities made available in excess of anticipated on-label demand or the use of channels of distribution particularly serving ''off-label'' users. Using the distribution of truthful and nonmisleading information to establish a law violation raises important First Amendment concerns about abridging freedom of speech. FDA has acknowledged the legitimacy of these First Amendment concerns by creating safe harbors for plain brown wrapper distribution of peer-reviewed journal publications and scientific responses to third-party initiated inquiries. FDA continues to insist, however, that all other forms of information dissemination can be considered as evidence of marketing for unapproved ''intended use,'' notwithstanding its recent failure to succeed in misbranding prosecutions relying on such dissemination in marketing efforts.

The fundamental schism between drug and device manufacturers who seek to limit their regulatory exposure to uses of their approved products they specifically advocate and federal regulators concerned about exposing patients to unevaluated drug and device uses has a long history and seems irreconcilable. There is, however, a possible avenue of ''off-label'' use reconciliation that could be explored in the one-year cooling off period FDA recently announced.

FDA has comprehensive regulatory authority over the form and content of the labeling of approved drugs and devices. Using that authority, FDA could require manufacturer/sellers to include an express warning that the labeled drug or device has been approved as safe and effective ONLY as set forth on the label and that there can be no assurance that it otherwise can be used safely and effectively. That warning would provide prescribers and patients clear notice that off-label use was at their peril. Moreover, where there was substantial evidence of potential harm from off-label use, the general warning could be enhanced to specify that risk.

An ''off-label'' warning solution would not foreclose FDA from taking regulatory action against manufacturer/sellers who actually advocate off-label use. It would, however, preclude imposing regulatory liability on manufacturer/sellers for decisions beyond their control made by prescribers and patients and it would permit the dissemination of scientific information on off-label use accompanied by the same disclaimer of safety and effectiveness approval. From FDA's perspective, a clear warning would facilitate responsible judgments by prescribers backed by the tort malpractice system, and preserve manufacturer/seller incentives to expand on-label uses by seeking FDA approval. Of course, in FDA's perfect world, all uses of drugs and devices would have been FDA approved. The speed of information dissemination in the modern world and the cost and delay inherent in FDA's approval process makes that goal unattainable despite FDA's attacks on off-label use, even if desirable. By focusing on enhanced and appropriately disclaimed off-label information flow, FDA would bring off-label use out of the shadow world and truly serve the public health.

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