

KEEPING THE LABEL OUT OF THE CASE

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INTRODUCTION

The FDA approves prescription drugs and medical devices for only the specific uses indicated in the product labeling that the manufacturer submits in the approval process. A physician may determine, however, that a use not indicated in the FDA-approved labeling—an “off-label” use—would benefit a patient. This Article argues that in medical malpractice cases involving an off-label use, the product’s label should not be admitted as evidence of either the standard of care or the physician’s alleged breach of that standard.

I. OFF-LABEL USE EXPLAINED

A. *The FDA Approves Drugs and Devices for Only Specified “Intended Uses”*

Prescription drugs and certain medical devices cannot be sold and marketed in the United States unless the Food and Drug Administration (“FDA”) approves them.¹ The FDA approval regimes for drugs and medical devices require manufacturers to submit proposed labeling.² This labeling must include, among other things, indications of the product’s intended use, such as the conditions it treats, the appropriate patient population, and

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¹ See, e.g., 21 U.S.C. §§ 355 (drugs) (link), 360e (devices) (link) (2006). The FDA drug and device approval regimes are discussed in detail in James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 FOOD & DRUG L.J. 71, 72–76 (1998).

² E.g., 21 U.S.C. §§ 355(b)(1) (drugs), 360e(c)(1)(F) (devices); 21 C.F.R. § 314.50(c)(2)(i) (2008) (drugs) (link).

administration and dosage information.³ When the FDA approves a drug or device for sale and marketing, it does so only with respect to the indicated uses.⁴

The FDA-approved label may also include “contraindications” and “warnings and precautions.” A “contraindication” is a “situation[] in which the drug should not be used because the risk of use . . . clearly outweighs any possible therapeutic benefit.”⁵ “Warnings and precautions” are descriptions of “clinically significant adverse reactions . . . , other potential safety hazards . . . , limitations in use imposed by them . . . , and steps that should be taken if they occur,” as well as any other “information regarding any special care to be exercised by the practitioner for safe and effective use of the drug”⁶

The analysis in this Article is limited to off-label uses that are not contraindicated, warned against, or identified by a precaution. In a medical malpractice action involving a use that is contraindicated, for example, the FDA-approved label should be admissible because the FDA has analyzed that very use and concluded that the associated risk is unacceptable.⁷ By contrast, in an action involving a use as to which the FDA-approved label is silent, the FDA has not reached the same conclusion. The FDA may simply not have considered the use being litigated, and the label listing the FDA-approved uses is therefore irrelevant to determining whether the standard of care has been met.

B. Off-Label Use Is Widespread

Although the FDA approves drugs and medical devices for only the uses indicated in the product labeling, drugs and devices may have other, off-label uses that are beneficial.⁸ For example, physicians may use a product to treat a disease other than the one (or ones) the drug or device was ap-

³ *E.g.*, 21 C.F.R. §§ 201.56(d)(1) (link), 201.57(c)(2)–(3) (drugs) (link), 801.109 (devices) (link) (2008).

⁴ *See, e.g.*, 21 U.S.C. §§ 355(d) (drugs), 360e(d)(1)(A)(ii), 360e(d)(2)(A)–(B) (devices). *Cf.* 21 C.F.R. § 201.57(c)(2)(ii) (“If there is a common belief that [a] drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective or that the therapeutic benefits . . . do not generally outweigh its risks, FDA may require [a statement] that there is a lack of evidence that the drug is effective or safe for that use or condition.”).

⁵ 21 C.F.R. § 201.57(c)(5).

⁶ *Id.* § 201.57(c)(6)(i)–(ii).

⁷ For the same reason, in a medical malpractice case involving an “on-label” use, the prescribing physician should be allowed to offer the label as evidence that the FDA has considered that use and determined it to be safe and effective. *See* James R. Bird, Comment, *Package Inserts for Prescription Drugs as Evidence in Medical Malpractice Suits*, 44 U. CHI. L. REV. 398, 445–46 (1977). This Article does not address what, if any, evidence plaintiffs may offer to try to offset that showing.

⁸ *See, e.g.*, MayoClinic.com, Off-Label Drugs and Medical Devices: Get the Facts, <http://www.mayoclinic.com/health/off-label/DI00088> (last visited Apr. 2, 2009) (link).

proved to treat.⁹ Or, physicians may prescribe a drug or device for a person outside the approved patient population.¹⁰ Physicians may also administer drugs by different routes, or in different doses or frequency, than approved by the FDA.¹¹

Off-label use of drugs and medical devices is common. Between twenty-five and sixty percent of all drug prescriptions written may be for off-label uses.¹² For some conditions, the percentage is even higher. One report estimates that sixty-five percent of all cancer drug use is off-label.¹³ Other studies estimate that seventy percent of kidney dialysis patients use their equipment off-label,¹⁴ and that more than eighty percent of AIDS patients are receiving at least one off-label drug treatment.¹⁵

II. THE FDA-APPROVED DRUG OR DEVICE LABEL SHOULD NOT BE ADMITTED IN AN OFF-LABEL USE CASE

Virtually all medical treatments carry some degree of risk.¹⁶ When a physician treats a patient with an off-label use and the patient is injured in

⁹ *Id.*

¹⁰ *Id.*

¹¹ *Id.*; Lars Noah, *Constraints on the Off-Label Uses of Prescription Drug Products*, 16 J. PROD. & TOXICS LIAB. 139, 140–41 (1994).

¹² Beck & Azari, *supra* note 1, at 80; Noah, *supra* note 11, at 139.

¹³ U.S. GEN. ACCOUNTING OFFICE, PROGRAM EVALUATION & METHODOLOGY DIV. NO. 91-14, OFF-LABEL DRUGS: REIMBURSEMENT POLICIES CONSTRAIN PHYSICIANS IN THEIR CHOICE OF CANCER THERAPIES 13 (1991) [hereinafter GAO REPORT], available at <http://archive.gao.gov/d18t9/144933.pdf> (link). See also, e.g., P. G. Casali, *The Off-Label Use of Drugs in Oncology: A Position Paper by the European Society for Medical Oncology (ESMO)*, 18 ANNALS ONCOLOGY 1923, 1923 (2007) (internal citations omitted) (“The off-label use of drugs in oncology has been estimated to reach 50%, or even more.”) (link).

¹⁴ *FDA and Dialyzer Makers Spar Over Device Reuse*, FOOD & DRUG LETTER, Apr. 8, 1994, at 3.

¹⁵ Carol L. Brosgart et al., *Off-Label Drug Use in Human Immunodeficiency Virus Disease*, 12 J. ACQUIRED IMMUNE DEFICIENCY SYNDROMES & HUMAN RETROVIROLOGY 56, 57–58 (1996). Other conditions with standard off-label use treatments have included heart and circulatory disease, osteoporosis, spinal injuries requiring fusion surgery, and incontinence. Beck & Azari, *supra* note 1, at 80 & n.80. Because historically drugs were rarely tested on children, the FDA rarely had the data necessary to approve drugs for use on children. Thus, as many as eighty percent of prescriptions written for children were for off-label uses. See, e.g., Lauren Hammer Breslow, Note, *The Best Pharmaceuticals for Children Act of 2002: The Rise of the Voluntary Incentive Structure and Congressional Refusal to Require Pediatric Testing*, 40 HARV. J. ON LEGIS. 133, 135–44 (2003) (analyzing reasons for the scarcity of pediatric clinical drug trials) (link). Since 1997, Congress has passed a series of measures to increase pediatric testing and labeling of drugs and devices. See, e.g., Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 111, 111 Stat. 2296, 2305–09 (1997) (codified as amended at 21 U.S.C. § 355a (2006) (link)) (link). These measures, however, have been voluntary, subject to waiver, and/or applied primarily to new drugs and devices, and some of the provisions are relatively new. Thus, it is not clear that they have significantly affected the frequency of off-label pediatric uses.

¹⁶ See, e.g., U.S. Food and Drug Administration, Information for Consumers: Side Effects, http://www.fda.gov/cder/info/consumer_safety.htm (last visited Apr. 2, 2009) (“All medicines have benefits and risks.”) (link).

the course of that treatment, the patient may sue and contend that the off-label use was, in and of itself, a violation of the standard of care—that such use was negligent.¹⁷ Undoubtedly, the patient will try to introduce the drug’s or device’s label as evidence of the physician’s alleged negligence.

One recent case reported that “[v]irtually every court addressing [the] question has concluded that the drug’s labeling and PDR reference are relevant to the standard of care issue.”¹⁸ According to that court, “[s]everal jurisdictions, believing drug manufacturers to be uniquely knowledgeable about the proper use of their products, have held that a drug’s labeling or its parallel PDR reference amounts to prima facie evidence of the standard of care as far as the use of that drug is concerned.”¹⁹ Nevertheless, “a majority of jurisdictions have determined that a prescription drug’s labeling or parallel PDR reference is admissible to prove the standard of care, but only if the plaintiff also introduces other expert testimony regarding the standard of care.”²⁰

Both rationales for admitting drug and device labeling in off-label use cases are incorrect. FDA-approved drug and device labeling is not relevant evidence of the standard of medical care. And even if the labeling offered *some* evidence of that standard, the risk of confusion, prejudice, and undue waste of time would substantially outweigh that marginal relevance.

A. *The FDA-Approved Label Is Not Relevant Evidence of the Standard of Care*

The plaintiff in a medical malpractice action must prove that the defendant physician failed to meet the standard of care, which in most jurisdictions is the level of skill and knowledge possessed by medical professionals in the same or a similar community.²¹ Only evidence that is relevant to establishing the standard of care should be admitted in the plaintiff’s case. The FDA-approved label is not relevant evidence of the standard of care in an off-label use case for several reasons.

¹⁷ See Paul D. Rheingold & David B. Rheingold, *Offense or Defense? Managing the Off-Label Use Claim*, 37 TRIAL, Mar. 2001, at 52, 52–55.

¹⁸ *Richardson v. Miller*, 44 S.W.3d 1, 15 (Tenn. Ct. App. 2000) (link). “PDR” refers to the PHYSICIANS’ DESK REFERENCE, “an encyclopedia of medications written and published annually and provided to all practicing physicians.” *Id.* at 11. The PDR contains the same information drug manufacturers are required to include in their package insert labeling. *Id.*; see 21 C.F.R. § 201.100(c)–(d) (2008) (link).

¹⁹ *Richardson*, 44 S.W.3d at 16 (citing cases).

²⁰ *Id.* The treatment of drug and device labels in medical malpractice cases is also discussed in Bird, *supra* note 7.

²¹ See, e.g., RESTATEMENT (SECOND) OF TORTS § 299A (1965) (“[O]ne who undertakes to render services in the practice of a profession or trade is required to exercise the skill and knowledge normally possessed by members of that profession or trade in good standing in similar communities.”).

1. *The FDA and Manufacturers Are Not Local Medical Practice Standard Bearers*

Drug and device labeling is a creature of federal regulatory law. The FDA, the creature's master, has repeatedly said it does not regulate the practice of medicine.²² Accordingly, the FDA has repeatedly confirmed that the absence of a particular use from a drug's or device's approved label has no legal effect on a physician's ability to put the drug or device to that use:

- In a 1972 rulemaking proposal, the FDA stated that a “physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the package insert”²³ Thus, “labeling is not intended either to preclude the physician from using his best judgment in the interest of the patient, or to impose liability if he does not follow the package insert.”²⁴
- In a 1982 *Drug Bulletin*, the FDA stated that federal law “does not . . . limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling.”²⁵
- In a January 2009 industry guidance document, the FDA stated that “[o]nce a drug or medical device has been approved or cleared by FDA, generally, health-care professionals may lawfully use or prescribe that

²² See, e.g., *More Information for Better Patient Care: Hearing on S. 1477 Before the S. Comm. on Labor and Human Resources*, 104th Cong. app. at 82 (1996) (statement of William B. Schultz, Deputy Comm’r for Policy, Food & Drug Admin.), available at <http://www.fda.gov/ola/1996/s1447.html> (arguing that “[t]he legislative history of the Federal Food, Drug, and Cosmetic Act indicates that Congress did not intend FDA to interfere with the practice of medicine,” and that “once a drug is approved for marketing, FDA does not generally regulate how, and for what uses, physicians prescribe that drug”) (link). The United States Supreme Court has reached the same conclusion. See *Buckman Co. v. Plaintiffs’ Legal Comm.*, 531 U.S. 341, 350 (2001) (stating that “‘off-label’ usage of medical devices (use of a device for some other purpose than that for which it has been approved by the FDA) is an accepted and necessary corollary of the FDA’s mission to regulate in this area without directly interfering with the practice of medicine”) (link).

²³ Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration, 37 Fed. Reg. 16,503, 16,503 (proposed Aug. 15, 1972) (link).

²⁴ *Id.* at 16,504. Notwithstanding this clear statement that an off-label use is not unlawful, the FDA also said in the same document that “labeling, along with medical articles, tests, and expert opinion, may constitute evidence of the proper practice of medicine” *Id.* (emphasis added).

²⁵ 12 FDA DRUG BULL., Apr. 1982, at 1, 5 (link).

product for uses or treatment regimens that are not included in the product's approved labeling"²⁶

Congress, too, recognizes that off-label uses are not *per se* improper. Federal law provides that “[n]othing in [the Federal Food, Drug, and Cosmetic Act] shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship.”²⁷ Also, Congress requires government insurance programs to pay for certain off-label uses.²⁸

Unsurprisingly, federal²⁹ and state courts³⁰ are in accord. And, like Congress, many state legislatures have at least tacitly approved certain off-label uses by requiring insurance companies to cover them.³¹

These positions make sense because the FDA's information-gathering role in the approval process is largely passive and static, relying generally

²⁶ FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: GOOD REPRINT PRACTICES FOR THE DISTRIBUTION OF MEDICAL JOURNAL ARTICLES AND MEDICAL OR SCIENTIFIC REFERENCE PUBLICATIONS ON UNAPPROVED NEW USES OF APPROVED DRUGS AND APPROVED OR CLEARED MEDICAL DEVICES 3 (2009) [hereinafter FDA, UNAPPROVED NEW USES REPRINT GUIDANCE], available at <http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0053-gdl.pdf> (link). It is particularly anomalous to admit the drug's labeling taken from the PDR, as some courts have done, because that publication recognizes that the FDA-approved labeling it contains does not “limit the manner in which a physician may use an approved drug.” *Foreword to PHYSICIANS' DESK REFERENCE* (62d ed. 2008).

²⁷ 21 U.S.C. § 396 (2006) (link).

²⁸ *E.g.*, 42 U.S.C. § 1395x(t)(2)(A)–(B) (2006) (including off-label indications supported by specified medical publications in Medicare reimbursement program) (link).

²⁹ *See, e.g.*, *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001); *Ortho Pharm. Corp. v. Cosprophar, Inc.*, 32 F.3d 690, 692 (2d Cir. 1994) (“[T]he FDA permits doctors to prescribe drugs for ‘off-label’ uses.”) (link); *Weaver v. Reagen*, 886 F.2d 194, 198 (8th Cir. 1989) (“[T]he fact that FDA has not approved labeling of a drug for a particular use does not necessarily bear on those uses of the drug that are established within the medical and scientific community as medically appropriate.”) (link).

³⁰ *See, e.g.*, *Sita v. Long Island Jewish-Hillside Med. Ctr.*, 803 N.Y.S.2d 112, 114 (N.Y. App. Div. 2005) (“Although marketing and promotion of the [treatment] system was not approved by the [FDA] for treating the injured plaintiff's condition, this does not prevent a physician from using the system in an ‘off-label’ manner.”) (link); *State Bd. of Regents for the Healing Arts v. McDonagh*, 123 S.W.3d 146, 150 (Mo. 2003) (“[N]on-FDA-approved, or ‘off-label,’ use of medications by physicians is not prohibited by the FDA and is generally accepted in the medical profession.”) (link); *Southard v. Temple Univ. Hosp.*, 781 A.2d 101, 104 (Pa. 2001) (“The FDA does not preclude off-label use of medical devices. To the contrary, while the FDA regulates the marketing and labeling of medical devices, it does not purport to interfere with the practice of medicine.”).

³¹ *E.g.*, ALA. CODE § 27-1-10.1 (LexisNexis 2007) (link); CAL. INS. CODE § 10123.195(a) (West 2005) (link); CONN. GEN. STAT. ANN. §§ 38a-492b(a) (link), 38a-518b(a) (link) (West 2007); FLA. STAT. ANN. § 627.4239(2)(a) (West 2005) (link); 5 ILL. COMP. STAT. ANN. 375/6.4 (West 2005) (link); MICH. COMP. LAWS ANN. §§ 500.3406e (link), 500.3616a (link) (West 2002); MO. ANN. STAT. §§ 376.429(3) (link), 376.1361(11) (link) (West 2002 & Supp. 2009); N.H. REV. STAT. ANN. §§ 415:6-g (link), 415:18-j (link) (LexisNexis 2009); N.J. STAT. ANN. § 26:1A-36.9 (West 2007) (link); OHIO REV. CODE ANN. § 1751.66(A) (West Supp. 2008) (link); OKLA. STAT. ANN. tit. 63, §§ 1-2604, 1-2605 (West 2004) (link); R.I. GEN. LAWS § 27-55-2 (2008) (link); VA. CODE ANN. § 38.2-3407.5 (2007) (link).

on only data that exists when approval is sought and for indications that the manufacturer chooses to pursue.³² A physician, by contrast, has “access to new information on drugs through the medical literature, scientific meetings, postgraduate courses, and professional contacts with colleagues.”³³ Thus, “[t]he package insert is not intended under the law to serve as a totally current repository of all such information.”³⁴

Drug and device manufacturers likewise are not attempting to define the standard of care. They prepare labeling to get their products approved and to market.³⁵ Thus, courts have found that “[t]he purposes behind the [information a drug or device manufacturer provides about a product] render its contents ill-suited to serve as prima facie evidence of a standard of care; they seek to cover a wide range of concerns not always directed at a diagnosis and course of treatment.”³⁶

2. *There Are Many Reasons, Unrelated to Standards of Care, Why a Use May Not Be Indicated “On Label”*

The uses indicated in a drug’s or device’s FDA-approved labeling are not evidence that another use is outside the standard of care because there are compelling reasons why a widely accepted and demonstrably safe and effective use for a drug or device may be omitted. For one, science advances more quickly than regulation.³⁷ Physicians may discover the bene-

³² An FDA official has observed that, in some cases, the existing data regarding an off-label use is sufficiently comprehensive that the use “could be approved by FDA if the sponsor would simply compile the existing literature and submit it to us.” *More Information for Better Patient Care: Hearing on S. 1477 Before the S. Comm. on Labor & Human Res.*, 104th Cong. app. at 88 (1996) (statement of William B. Schultz, Deputy Comm’r for Policy, Food & Drug Admin.), available at <http://www.fda.gov/ola/1996/s1447.html> (link).

³³ Labeling for Prescription Drugs Used in Man: Proposed Format of Prescription-Drug Advertisements, 40 Fed. Reg. 15,392, 15,394 (proposed Apr. 7, 1975).

³⁴ *Id.* Courts have also recognized the limitation. See, e.g., *United States v. Evers*, 453 F. Supp. 1141, 1149 (M.D. Ala. 1978) (“It is well-recognized that a package insert may not contain the most up-to-date information about a drug . . .”) (link). After the FDA approves a drug or device for an indicated use, it continues to monitor adverse events and may withdraw its approval if it determines that the drug or device is not safe for that use. See, e.g., 21 C.F.R. §§ 314.80 (link), 314.150 (link) (2008). The FDA will not, however, act to approve a new use unless the manufacturer submits the appropriate supporting information. See *supra* note 32 and accompanying text.

³⁵ E.g., *Arnold v. Lee*, No. 05-0651, 2006 WL 1410161, at *4 (Iowa Ct. App. May 24, 2006) (stating that “the manufacturer has its own reasons for the information contained in the package inserts,” which “are not limited to altruism or the education of the medical community”). See also Bird, *supra* note 7, at 416 (noting that the American Medical Association “has repeatedly alleged that inserts are an inadequate standard for medical practice, pointing to the inconsistent purposes served by the document—advertising for the manufacturer, regulation by the government, and information for the doctor”).

³⁶ *Spensieri v. Lasky*, 723 N.E.2d 544, 548 (N.Y. 1999) (internal citations omitted) (link).

³⁷ E.g., *Sidney A. Shapiro, Limiting Physician Freedom to Prescribe a Drug for Any Purpose: The Need for FDA Regulation*, 73 NW. U. L. REV. 801, 811 (1978) (observing that off-label uses “are unlikely ever to be eliminated since there is an unavoidable lag between the time a new use for a drug is discovered and the time that use is approved by the FDA”). Indeed, a manufacturer may not even start the

fits of an off-label use and share those benefits with others, through journals, presentations, and professional associations, long before the FDA approves the use.³⁸

Even if science and regulation advanced at the same rate, however, there are several reasons why much standard of care medicine would still not be reflected in drug or device labeling.³⁹ First, “[b]ecause of the time and expense of obtaining FDA approval of new uses for an already approved drug, drug manufacturers frequently do not voluntarily request FDA approval for a new use unless the change in the labeling will pay for itself in increased profits.”⁴⁰ Self-funding label changes are particularly unlikely when the drug’s or device’s patent is nearing expiration (thus exposing the drug or device to generic competition)⁴¹ and when the market for the off-label use is small.⁴²

Second, drug and device manufacturers have limited research and development dollars, and they may decide those dollars are better spent pursuing groundbreaking new therapies than seeking approval for new uses of products already being sold.⁴³

Third, limited resources may also make it difficult for manufacturers to find researchers willing to perform the clinical trials necessary to obtain FDA approval for the new use. When the off-label use to be investigated is already widely accepted, researchers may find the investigation to be “at least uninteresting, if not a waste of time.”⁴⁴

Fourth, when the off-label use is already widely accepted as beneficial, the availability of researchers may also be limited by ethical constraints: “The conflict between the patient’s therapeutic needs and the needs of the experimental trial [such as supplying placebos to the control group of afflicted subjects] poses ethical problems which may deter a physician from acting as an investigator.”⁴⁵

testing required to support FDA approval for a new use until after that use becomes the medically accepted standard. *Id.*

³⁸ See 12 FDA DRUG BULL., *supra* note 25, at 5.

³⁹ See Stuart L. Nightingale, *Off-Label Use of Prescription Drugs*, 68 AM. FAM. PHYSICIAN 425, 425–26 (2003) (link).

⁴⁰ *Richardson v. Miller*, 44 S.W.3d 1, 12 (Tenn. Ct. App. 2000). The General Accounting Office similarly observed that, when an off-label use is proven effective, “the manufacturer can ask the FDA to make a formal change in the label that would reflect the expanded benefits of the drug. However, representatives from the pharmaceutical industry characterize this process as cumbersome, time-consuming, and expensive compared to the payoff for a company.” GAO REPORT, *supra* note 13, at 11 n.2.

⁴¹ See GAO REPORT, *supra* note 13, at 11 n.2.

⁴² See, e.g., Beck & Azari, *supra* note 1, at 80 n.80 (observing that “[m]ost diseases afflicting fewer than 200,000 Americans” do not have FDA-labeled treatments).

⁴³ Noah, *supra* note 11, at 145.

⁴⁴ David A. Kessler, *Regulating the Prescribing of Human Drugs for Nonapproved Uses Under the Food, Drug, and Cosmetic Act*, 15 HARV. J. ON LEGIS. 693, 730 (1978).

⁴⁵ *Id.*; see Jennifer A. Henderson & John J. Smith, *Realizing the Potential for Biomarkers in Imaging: Background and Legal Basis*, 60 FOOD & DRUG L.J. 511, 515–16 (2005) (link).

Fifth, when the off-label use is already the standard of care for a particular disease or condition, it may be difficult to find a traditional control group, because most people afflicted with the disease or condition are already receiving the off-label treatment that is to be studied.⁴⁶

Sixth, if a manufacturer seeks approval for a new use, the FDA may choose to revisit the entire label.⁴⁷ If the original label resulted from compromise between the manufacturer and the FDA, the manufacturer may wish not to reopen these negotiations.⁴⁸

Congress's efforts to induce manufacturers to seek FDA approval for off-label uses have not entirely cured these disincentives. Although manufacturers are not permitted to market a drug for off-label use, the 1997 Food and Drug Administration Modernization Act allowed manufacturers to disseminate certain scientific literature about an off-label use if the manufacturer had submitted, or certified that it would submit, a supplemental application seeking FDA approval for the use.⁴⁹ The statute permitted manufacturers to disseminate information without submitting, or promising to submit, a supplemental application, however, when it would be "economically prohibitive . . . to conduct the studies necessary to submit a supplemental application for the [off-label] use."⁵⁰ And, of course, manufacturers willing to rely on the medical community to spread the word about a particular off-label use would not subject themselves to this rule. In any case, this provision and its implementing regulations expired in 2006.⁵¹ The FDA recently issued an industry guidance statement on the topic, which suggests that manufacturers may continue to disseminate certain types of literature about off-label uses, but without requiring manufacturers to submit, or promise to submit, a supplemental application for FDA approval of those uses.⁵²

Thus, there are many reasons—unrelated to the standard of care—why certain uses of a drug or device would not be indicated in the FDA-approved labeling.

⁴⁶ Henderson & Smith, *supra* note 45, at 515–16.

⁴⁷ Shapiro, *supra* note 37, at 812 n.77.

⁴⁸ *Id.*; see Kessler, *supra* note 44, at 723–24.

⁴⁹ See Pub. L. No. 105-115, § 401(a), 111 Stat. 2296, 2356–63 (1997) (codified as amended at 21 U.S.C. §§ 360aaa–360aaa-6) (expired 2006) (link).

⁵⁰ 21 C.F.R. § 99.205(b) (2008) (link). To qualify for this exemption, the manufacturer must explain why the data in the disseminated study are not sufficient to support the supplemental application and present evidence that the cost of the studies necessary to support the supplemental application exceeds the expected net revenues from the off-label use. *Id.* § 99.205(b)(1)(i)–(ii).

⁵¹ Food and Drug Administration Modernization Act, § 401(e), 111 Stat. at 2364 (link); FDA, UNAPPROVED NEW USES REPRINT GUIDANCE, *supra* note 26, at 2.

⁵² FDA, UNAPPROVED NEW USES REPRINT GUIDANCE, *supra* note 26, at 2–6.

3. *Off-Label Use May Actually Be the Standard of Care*

An FDA-approved label should not be admissible as evidence of the standard of care because the FDA, as well as leading medical authorities and courts, have recognized that an off-label use may well be the safest, most effective, state-of-the-art treatment. Indeed, the off-label use may itself constitute the standard of care. For example:

- The FDA, in an industry guidance document, which represents the FDA's "current thinking," observes that "off-label uses or treatment regimens . . . may even constitute a medically recognized standard of care."⁵³
- The General Accounting Office's Director of Health Services Quality and Public Health Issues testified to a congressional subcommittee that "a drug given off-label may have been proven to be safer and more beneficial than any drug labeled for that disease."⁵⁴
- Courts have found that "[b]ecause the pace of medical discovery runs ahead of the FDA's regulatory machinery, the off-label use of some drugs is frequently considered to be 'state-of-the-art' treatment." Indeed, "[i]n some circumstances, an off-label use of a particular drug or device may even define the standard of care."⁵⁵
- According to the vice president of the American Medical Association, "[i]n some cases, if you didn't use the drug in the off-label way you'd be guilty of malpractice."⁵⁶

Neither the FDA nor manufacturers intend to set the standard of care for medical malpractice purposes in drug and device labeling. There are many reasons why uses that conform to the standard of care may be omitted from an FDA-approved label. An FDA-approved label's silence as to a particular use is therefore evidence of nothing in an off-label medical malpractice case.

⁵³ *Id.* at 3.

⁵⁴ *Off-Label Drug Use and FDA Review of Supplemental Drug Applications: Hearing Before the Subcomm. on Human Resources and Intergovernmental Relations of the H. Comm. on Government Reform and Oversight*, 104th Cong. 12 (1996) (statement of Sarah F. Jaggard, Director of Health Services Quality and Public Health Issues, Health, Education, and Human Services Division, Gen. Accounting Office) (link).

⁵⁵ *E.g.*, *Richardson v. Miller*, 44 S.W.3d 1, 13 n.11 (Tenn. Ct. App. 2000).

⁵⁶ Fran Kritz, *FDA Seeks to Add Drugs' New Uses to Labels*, WASH. POST, Mar. 29, 1994, at Z11.

B. Admitting Drug and Device Labels Poses a Substantial Risk of Prejudice and Confusion

Some courts have admitted FDA-approved drug and device labels as “some evidence” of the standard of care.⁵⁷ For all the reasons explained above, those courts decided wrongly. But even if FDA-approved labels had *some* evidentiary value in an off-label use case, that value would be outweighed by the significant risk of prejudice, confusion, and time-wasting that its admission would cause.⁵⁸

Indeed, just the terminology associated with off-label use poses the risk of prejudice and confusion. Uses of drugs and devices not indicated on the drug’s or device’s labeling can be called “unapproved,” “unlabeled,” “off-label,” or “extra-label.”⁵⁹ As the FDA itself recognized, “[t]he term ‘unapproved uses’ is, to some extent, misleading. It includes a variety of situations ranging from unstudied to thoroughly investigated drug uses.”⁶⁰

Consumer survey data confirm these risks. According to a 2006 *Wall Street Journal/Harris Interactive Health-Care* Poll, fifty percent of adults in the United States (out of 3,018 surveyed) believe that, once a drug is approved by the FDA, a physician may prescribe the drug for only the FDA-approved uses; another twenty-five percent were unsure.⁶¹ A trial laden with references to “unapproved” uses would also inappropriately pander to jurors’ views that off-label uses should not be permitted. The same survey found that nearly half of respondents believe that physicians should not be allowed to prescribe a drug to treat diseases other than the diseases indicated in the FDA-approved labeling for that drug.⁶² More respondents disagreed than agreed that “[d]octors should be allowed to decide which prescription drug treatments to use with their patients regardless of what diseases they have or have not been approved for by the FDA.”⁶³ And sixty-two percent of respondents agreed that “[p]rescription drug use for unapproved medical conditions should be prohibited except as part of the clinical research trial.”⁶⁴

⁵⁷ See, e.g., *supra* note 20 and accompanying text.

⁵⁸ See FED. R. EVID. 403 (link).

⁵⁹ Citizen Petition Regarding the Food and Drug Administration’s Policy on Promotion of Unapproved Uses of Approved Drugs and Devices; Request for Comments, 59 Fed. Reg. 59,820, 59,820 (Nov. 18, 1994) (link).

⁶⁰ 12 FDA DRUG BULL., *supra* note 25, at 5.

⁶¹ Harris Interactive News Room, U.S. Adults Ambivalent About the Risks and Benefits of Off-Label Prescription Drug Use (Dec. 7, 2006), <http://www.harrisinteractive.com/news/allnewsbydate.asp?NewsID=1126> (link).

⁶² *Id.*

⁶³ *Id.*

⁶⁴ *Id.*

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These 2006 results confirm the results of a similar survey conducted in 2004.⁶⁵ Together, these surveys demonstrate that public misconception and distrust about off-label use is common and deep-seated.

At least one court has, without the benefit of this type of survey data, concluded that the risk of confusion and prejudice could be adequately addressed through cross-examination and jury instructions.⁶⁶ But if either of those were a panacea, then Federal Rule of Evidence 403 and its state law analogues, which exclude evidence likely to confuse and more prejudicial than probative, would not be necessary. And the Harris Poll results demonstrate the sort of “widely held prejudice”⁶⁷ that courts have relied on to exclude evidence under those rules.⁶⁸

Evidence that a particular use is off-label should also be excluded to avoid wasting time.⁶⁹ Consider, for example, the case in which the plaintiff relies exclusively on the off-label nature of the use as proof of malpractice. If the physician’s expert witness will testify that the off-label use was, in fact, the state-of-the-art treatment, and the judge will instruct the jury that an off-label use is not negligence *per se*, then the label would come in, only to be refuted by evidence that the physician and court hope will erase the label’s effect on the jurors. This wastes time and may breed confusion.

Even if the plaintiff offered expert testimony in addition to the product label to establish the standard of care, admitting the label would waste time. In a field such as oncology, for example,⁷⁰ the plaintiff would offer the label and the defense expert would testify that most treatments are off-label and so the uses indicated on the label are far removed from the standard of care. The physician in that type of case may or may not have committed malpractice, but admitting the label consumes time without giving the jury useful information.

CONCLUSION

Drug and device labels reflect competing regulatory and commercial interests. Because they are frozen in time, they may not reflect advances in

⁶⁵ The 2004 survey asked the same questions as the 2006 survey. Harris Interactive News Room, Many People Think that Drugs Should Only Be Prescribed Per FDA-Approved Use, Not for Off-Label Use (Jun. 9, 2004), <http://www.harrisi.org/news/allnewsbydate.asp?NewsID=808> (link). The chairman of the Harris Poll observed that these results indicated “massive public ignorance of “off-label prescribing.”” and that, notwithstanding the “several strong arguments in favor of off-label prescribing, . . . these data suggest that it is a potentially risky issue for both physicians and the pharmaceutical industry’” *Id.*

⁶⁶ Richardson v. Miller, 44 S.W.3d 1, 22 (Tenn. Ct. App. 2000).

⁶⁷ United States v. Kott, No. 3:07-cr-00056 JWS, 2007 WL 2461930, at *2 (D. Alaska Aug. 29, 2007).

⁶⁸ See, e.g., *id.* (excluding evidence that legislator had filed previous false *per diem* claims because it “would tend to support the widely held prejudice that many legislators are entirely corrupt”).

⁶⁹ See FED. R. EVID. 403.

⁷⁰ See *supra* note 13 and accompanying text.

the medical state-of-the-art. The FDA has repeatedly recognized that off-label uses are generally allowed and may be the standard of care. Thus, the absence of a use from an FDA-approved label proves nothing about the standard of care or a physician's deviation from (or adherence to) that standard when he or she employs that off-label use. Allowing plaintiffs in off-label medical malpractice cases to introduce evidence that the physician's use was "off-label," "unapproved," or "unauthorized" unfairly appeals to commonly held misconceptions about the effect of FDA approval. Defendants in these types of cases must know and use all the arguments available to oppose the admission of this off-label evidence, and courts must be made more aware of this evidence's prejudicial dangers.