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FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions

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I. INTRODUCTION

The recent fen/phen controversy[1] warrants revisiting the intersection of the doctrine of informed consent and the Food and Drug Administration's (FDA's) labeling authority, especially as the latter relates to medical treatments that employ drugs or medical devices for unindicated uses (off-label use).[2] This summer, the popular media discovered that the commonly prescribed combination of fenfluramine and phentermine was an off-label use. Both drugs had been approved separately for labeling and marketing for short-term use in weight reduction, but they often had been prescribed together for not only short-term, but long-term weight-loss treatment. Millions of people used one or more of the drugs.[3] Recent medical research reported an apparently abnormal incidence of heart valve disease among certain of these patients.[4] The research revealed an association between the incidence of such disease with fenfluramine — whether the drug was used as labeled or as part of the off-label combination — and FDA reacted by recalling the drug.[5]

The media, however, has focused on the fen/phen combination being an off-label use — neither drug's label mentioned their simultaneous use — although the use in combination has not been implicated in any increase in incidence of valvular disease. A misperception has arisen: people believe that if told the combination was off-label they would have known there was a risk in taking fen/phen. This perception is not true; it ignores evidence that the same statistical associations appear to be present

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The authors have represented manufacturers in various cases involving orthopedic bone screw product liability litigation. In connection with this representation, the authors became aware of, and interested in, informed consent issues that had been raised in the medical malpractice context against health-care providers in this litigation. The authors do not represent health-care providers in medical malpractice cases.

[1] *See, e.g.*, Laura Johannes & Steve Stecklow, *Withdrawal of Redux Spotlights Predicament FDA Faces on Obesity*, WALL ST. J., Sept. 16, 1997, at A1 (discussing recall of fenfluramine and dexfenfluramine after reports of incidents of heart valve damage).

[2] "Off-label" has more accurately been termed "extra label" use. It means only that a product is used for a condition or in a way not appearing on its FDA-regulated labeling, not that the agency has judged the use adversely. *See, e.g.*, Washington Legal Found. v. Kessler, 880 F. Supp. 26, 28 n.1 (D.D.C. 1995). *See infra* text accompanying notes 103-107. Off-label can mean many things. "[U]sing an approved drug to treat a disease that is not indicated on its label, but is closely related to an indicated disease, treating unrelated, unindicated diseases, and treating the indicated disease but varying from the indicated dosage, regimen, or patient population may all be considered off-label use." William L. Christopher, *Off-Label Drug Prescription: Filling the Regulatory Vacuum*, 48 FOOD & DRUG L. J. 247, 248 (1993) (footnotes omitted).

when fenfluramine (or a related drug, dexfenfluramine) is used alone and as labeled. The off-label nature of the combination thus does not seem to have anything to do with valvular disease.

The notion that off-label use is itself a "risk" is one of two common misperceptions addressed in this article. The second is that all off-label treatment is *ipso facto* "investigational" or "experimental." It is an accepted principle that once FDA determines that a drug or device can be marketed, a physician's discretionary use of that product (the practice of medicine) is not restricted to the uses indicated on FDA-regulated labels. Off-label use is widespread in the medical community and often is essential to giving patients optimal medical care, both of which medical ethics, FDA, and most courts recognize. Even so, the public (and an occasional court) mistakenly presumes that all off-label treatment is investigational or experimental and that physicians therefore should inform their patients of this whenever an off-label use is proposed.

All medical treatments, including off-label treatments, have medical risks;[6] and patients must be informed of medical risks. There is no question that patients should be advised if a proposed treatment is truly investigational or experimental, as those concepts are understood as a matter of medical ethics or food and drug law. The mere fact of off-label use, however, is a matter solely of FDA regulatory status and cannot logically be considered a medical risk of a drug or medical device. Nor is off-label use inherently experimental or investigational, the latter being an FDA term of art. Because FDA regulatory status of medical devices and drugs is irrelevant to the nature, risks, benefits, or alternatives of medical procedures, there is and should be no legal or ethical obligation for physicians to discuss FDA regulatory status issues with their patients. Expanding the doctrine of informed consent beyond medical matters — the nature of the treatment, how it may help the patient, what might go wrong, and possible alternative therapies — would confound patient decisionmaking by diverting attention to medically irrelevant information. In addition, such a rule would force physicians to learn and discuss legal/administrative (rather than medical) facts — potentially to their detriment and to the detriment of their patients. Rather than use FDA regulatory status as a sort of proxy (a seal of approval) for medical risks and benefits, the law quite properly requires physicians to discuss these issues with their patients directly.

This article begins by describing briefly how drugs and medical devices get to market, in order to delineate the clear regulatory distinction between investigational and off-label use. It then examines why physicians should not be required to include a legal discussion about FDA regulatory status in their informed consent discussions with patients. Finally, the article will consider how the Food and Drug Administration Modernization Act of 1997 (FDAMA)[7] will affect informed consent and off-label use.

II. TO MARKET, TO LABEL

A. *Medical Devices — 510(k) Clearance*

Medical devices can come to market in three familiar ways, each involving the presentation of detailed information to FDA for review. FDA can clear a device by

[6] Examples of off-label uses that have serious medical risks abound. *See, e.g.*, 62 Fed. Reg. 64,080-81 (Dec. 3, 1997).

[7] Pub. L. No. 105-115, 111 Stat. 2296 (1997).

finding it "substantially equivalent" to a device that either was in commercial distribution prior to passage of the Medical Device Amendments of 1976 (MDA)[8] to the Federal Food, Drug, and Cosmetic Act (FDCA),[9] or is otherwise being marketed legally.[10] The vast majority of devices are cleared for marketing this way, known as the 510(k) process.[11] Although the 510(k) process is the least time-consuming and arduous route to marketing a medical device,[12] this process was augmented considerably by the Safe Medical Devices Act of 1990.[13] Manufacturers must submit premarket notifications containing 1) proposed labeling; 2) a statement of design similarities and differences compared to the predicate device; 3) a description, which may include photographs and engineering drawings, of significant physical and performance characteristics of the device, including its design, materials, and physical properties; 4) the medical conditions for which the device is "intended" to be used; 5) information showing how the "design, material, chemical composition, or energy source" of the device is substantially equivalent to the predicate device; and 6) "[a]ny additional information" FDA requires to determine substantial equivalence.[14]

FDA exercises extensive control over the labeling of 510(k) devices. A 510(k) premarket notification must contain indications for use,[15] safety and effectiveness,[16] contraindications,[17] warnings,[18] precautions,[19] adverse reactions,[20] and special patient populations.[21] Prescription devices are subject to additional labeling requirements.[22]

B. *Medical Devices — Premarket Approval*

Manufacturers of medical devices that are not substantially equivalent to any preexisting device can seek FDA marketing approval through the more lengthy and rig-

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[8] Pub. L. No. 94-295, 90 Stat. 539 (1976).

[9] Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended 21 U.S.C. §§ 301 et seq. (1994)).

[10] 21 U.S.C. §§ 360(k) (section 510(k) of the MDA), 360c(f),(i) (detailing 510(k) criteria); 21 C.F.R. §§ 807.81- 807.100 (1997).

[11] *See* Medtronic, Inc. v. Lohr, 518 U.S. 470, ___, 116 S. Ct. 2240, 2247 (1996).

[12] *Id.*

[13] Pub. L. No. 101-629, 104 Stat. 4511 (1990).

[14] *See* 21 C.F.R. §§ 807.87(e)-(h), 807.92(a)(4)-(6).

[15] Indications for use include 1) the medical conditions for which use is indicated; 2) the target population; 3) whether the intended use is curative, palliative, or diagnostic; and 4) special instructions for long-term use. In the indications, FDA may require specific disclaimers of effectiveness for particular medical conditions. *See* Device Labeling Guidance, FDA Guidance Doc. No. G-91, pt. III (May 8, 1991).

[16] Safety and effectiveness information includes 1) the population of device users, 2) each medical condition that either the labeling or advertising suggests as a use for the device, 3) relative benefits and risks, and 4) reliability. *Id.*

[17] Contraindications involve all situations in which the risk of a device outweighs any possible benefit. *Id.* pt. IV.

[18] Warnings include all serious adverse reactions, potential safety hazards, and limitations on use, as well as the steps to be taken if such a risk occurs. A warning about an off-label use also may be "appropriate" if FDA considers the use both unproven and associated with a serious risk. *Id.* pt. V.

[19] Precautions mean 1) protective clothing, 2) special laboratory tests, or 3) any other particular procedures needed for the safe and effective use of the device. *Id.* pt. VI.

[20] Adverse reactions include any undesirable effects associated with use of the device, as well as the steps to be taken if such an effect occurs. *Id.* pt. VIII.

[21] The manufacturer must advise of concerns unique to users such as 1) pregnant women, 2) children, or 3) patients with anatomic or physiological limitations. *Id.* pt. VII.

[22] For example, prescription device labeling must state its prescription-only status and include "information for use including indications, effects, routes, methods, frequency and duration of administration, and any relevant hazards, contraindications, side effects and precautions" for "all purposes for which it is advertised or represented." *Id.* pt. IX. *See* 21 C.F.R. §§ 801.109(c), (d), 801.15.

orous premarket approval (PMA) process.[23] The PMA process requires a manufacturer to submit all design and labeling information necessary under the 510(k) process and more, because there is no history of an equivalent predicate device to serve as an indicator of safety and effectiveness. For example, the PMA process requires submission of 1) "full reports of all information, published or known" concerning clinical investigations and nonclinical studies performed for the product and their conclusions, whether adverse or supportive;[24] 2) the device's marketing history in the United States and abroad;[25] and 3) manufacturing quality control mechanisms.[26] It can take years before premarket approval is given, and the PMA process is much more costly to the manufacturer.[27]

C. *Medical Devices — Investigational Device Exemption*

A manufacturer can seek an exemption from the requirement that in order for a device to be distributed it must have 510(k) clearance or a PMA, by applying for an investigational device exemption (IDE).[28] The IDE process acts as an adjunct to an anticipated PMA application by allowing otherwise entirely unapproved/uncleared devices to be used in order for their safety and effectiveness to be investigated. The IDE process subjects the device to clinical trials governed by FDA regulations uniquely applicable to investigational devices — defined as those undergoing the investigation.[29] A "clinical investigation" is "any experiment that involves a test article and one or more human subjects."[30] This route to limited investigational marketing is quite different from the 510(k) and PMA processes. When an IDE device has no prior 510(k) clearance or PMA approval,[31] only volunteer patients (research subjects)[32] will have access to the IDE device, and only through a physician who voluntarily agrees to be an investigator[33] and to follow a protocol submitted to FDA by the manufacturer sponsor.[34] An independent institutional review board (IRB) supervises clinical trials.[35] The stringent and pervasive IDE regulations apply only to these FDA-approved investigations.[36]

A unique feature of the IDE process is the mandatory informed consent require-

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[23] 21 U.S.C. § 360e; 21 C.F.R. §§ 814.1 - 814.84. The premarket approval process often takes much longer than the 510(k) process. *See* Tim Friend, *Divided Over Devices, FDA Rules Force Medical Tests Overseas*, USA TODAY, May 10, 1995, at A1 (PMA approval to market shoulder implant already marketed in Europe may take seven years).

[24] 21 U.S.C. § 360e(c); 21 C.F.R. § 814.20(b)(3)(i). If the manufacturer has data from only one clinical investigation, the manufacturer must show that one investigation is sufficient to demonstrate the safety and effectiveness of the device. 21 C.F.R. § 814.20(b)(7).

[25] 21 C.F.R. § 814.20(b)(3)(iv).

[26] *Id.* § 814.20(b)(4)(v).

[27] *See supra* note 23.

[28] 21 U.S.C. § 360j(g); 21 C.F.R. pt. 50; 21 C.F.R. §§ 812.1 - 812.150.

[29] 21 C.F.R. § 812.3(g).

[30] *Id.* § 50.3(c).

[31] On the other hand, a device can both be marketed generally pursuant to a pre-existing 510(k) or PMA, while also being the subject of an IDE clinical trial for an additional intended use. Femrite v. Abbott Northwestern Hosp., 568 N.W.2d 535, 541 (Minn. Ct. App. 1997). In this circumstance the use being investigated by the IDE may be (and often is) simultaneously a popular off-label use. *See infra* text accompanying notes 69-85.

[32] 21 C.F.R. § 50.3(g).

[33] *Id.* § 50.3(d).

[34] *Id.* §§ 50.3(e), 812.110, 812.150.

[35] *Id.* § 50.3(i).

[36] *Id.* § 812; *id.* pts. 50 ("this part applies to all clinical investigations regulated by the [FDA]"), 56.

ment applicable to sponsors,[37] IRBs,[38] and investigators.[39] FDA's IDE regulations establish the circumstances under which an investigator shall obtain informed consent.[40] Under IDE regulations, there must be a written informed consent document including a statement that the study involves research; descriptions of any reasonably foreseeable risks, discomforts, or benefits; alternative procedures; confidentiality issues about the subject's medical records; explanation of compensation; treatments available for possible injuries arising from research involving more than "minimal" risk; and a statement that participation is voluntary and that the subject may discontinue participation without penalty.[41] Additional information is to be given "when appropriate."[42]

D. *Drugs — Investigational New Drugs and New Drug Applications*

FDA approval to market new drugs involves procedures similar to, and as extensive as, the IDE and PMA processes for medical devices.[43] A new drug first undergoes three phases of clinical testing through the investigational new drug (IND) process.[44] Under IND regulations, a sponsor submits a clinical testing plan, investigators (physicians) agree to perform clinical testing, volunteers agree to become subjects, and an IRB supervises the clinical investigation, just as is done for IDE medical devices.[45] Sponsors, IRBs, and investigators bear responsibility for obtaining the same specific informed consent required for an IDE medical device.[46]

If IND testing successfully demonstrates a drug's safety and effectiveness,[47] a manufacturer then may submit a new drug application (NDA) including the results of IND clinical tests for FDA review.[48] The NDA process for drugs and the PMA process for medical devices are in many ways analogous. Manufacturers submit detailed applications containing, for example, a list of all the components of the drug, detailed

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[37] *Id.* §§ 812.2(b)(1)(iii), 812.150(b)(8).

[38] *Id.* §§ 50.27, 56.109 (b), (c).

[39] *Id.* §§ 50.25, 812.150(a)(5).

[40] An investigator must give a prospective subject "sufficient opportunity to consider whether or not to participate" under circumstances that "minimize the possibility of coercion or undue influence." *Id.* § 50.20. The information must be in "language understandable to the subject." *Id.* The informed consent form cannot contain any "exculpatory language" that would "waive any of the subject's legal rights." *Id.* There is an "emergency" exception that permits the investigator to forego informed consent under dire, life-threatening circumstances. *Id.* §§ 50.23, 50.24. There also is a limited military exception, *id.* §§ 50.23, 50.24, that was exercised during the Persian Gulf War. *See* Nelson Borelli et al., *The Nuremberg Code, Informed Consent and Involuntary Treatment*, 277 JAMA 712 (1997) (military use without informed consent of investigational drug pyrisdostigmine).

[41] 21 C.F.R. § 50.25(a).

[42] *Id.* § 50.25(b).

[43] Similar to the 510(k) clearance process, there is an abbreviated application process available for drugs that are identical to certain drugs already marketed. *See id.* § 314.92. Both medical devices and drugs have compassionate use exemptions for life-threatening illnesses with no other treatments. *Id.* §§ 312.34, 312.80 - 312.88, 812.36.

[44] *Id.* §§ 312.1 - 312.70, 312.110 - 312.145.

[45] *Id.* §§ 312.53(c)(d) (sponsor's informed consent responsibilities pursuant to part 50), 312.60 (investigator's responsibility to obtain informed consent pursuant to part 50), 312.66 (IRB to act pursuant to part 56). *See also id.* § 312.88 ("All of the safeguards incorporated within parts 50, 56, 312, 314 and 600 . . . apply to drugs covered by this section. This includes the requirements for informed consent . . . and institutional review boards.").

[46] *See supra* note 45.

[47] For an analysis of safety to effectiveness ratios, see BARUCH A. BRODY, ETHICAL ISSUES IN DRUG TESTING, APPROVAL, AND PRICING 161-62 (1995).

[48] 21 C.F.R. §§ 314.1 - 314.560.

chemical information, detailed biological information (e.g., known mechanisms of resistance to the drug and metabolic information), summaries of clinical testing and conclusions, a summary of risks and benefits of the drug (including "a discussion of why the benefits exceed the risks"),[49] environmental impact statement, marketing history, and proposed labeling.[50]

Labeling requirements for drugs are as comprehensive as for medical devices — in some ways more so.[51] After FDA approves an NDA, the drug can be marketed for the uses for which it was investigated and labeled.[52] FDA continues to monitor a drug after it is cleared for marketing, and can order labeling changes or can seek a complete recall (as the agency did with fenfluramine and dexfenfluramine).[53]

III. OFF-LABEL USES AND INFORMED CONSENT

A. *Off-Label Use is Legal, Common, and Necessary*

FDA never has had authority to regulate the practice of medicine; physicians may use legally marketed drugs or devices in any way that they believe, in their professional judgment, will best serve their patients.[54] Courts have repeatedly recognized the propriety of off-label use,[55] and several states statutorily recognize off-label use in various contexts.[56] New Jersey is typical of such states, in that it requires medical

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[49] *Id.* § 314.50(c)(5)(vi)(b)(viii).

[50] *Id.* § 314.50.

[51] *Id.* §§ 201.1 - 201.320.

[52] *See* David A. Kessler, *The Regulation of Investigational Drugs*, 420 NEW ENG. J. MED. 281-88 (1989); BRODY, *supra* note 47, at 161. There are exceptions to the NDA process allowing for expedited approval of investigational drugs for compassionate use. *Id.* at 174-77.

[53] *See* Health Advisory on Fen/Phen, *supra* note 4 ("the agency is notifying manufacturers to meet with FDA to discuss possible labeling changes"); FDA Withdrawal, *supra* note 5 (FDA "has asked the manufacturers to voluntarily withdraw" fenfluramine and dexfenfluramine. "The FDA is not requesting the withdrawal of phentermine.").

[54] *See, e.g., Femrite*, 568 N.W.2d at 539 n.4; Klein v. Biscup, 673 N.E.2d 225, 231 (Ohio Ct. App.), *appeal denied*, 667 N.E.2d 987 (Ohio 1996); Piazza v. Myers, 33 Phila. Co. Rptr. 144, 148 (Pa. C.P. Philadelphia Co. 1997); *see also In re* Orthopedic Bone Screw Products Liability Litigation, MDL No. 1014, 1996 WL 107556, at *3 (E.D. Pa. Mar. 8, 1996) ("the decision whether or not to use a drug for an off-label purpose is a matter of medical judgment, not of regulatory approval") (citation and quotation marks omitted). The FDCA was "not intended as a medical practices act and [did] not interfere with the practice of the healing art." S. REP. No. 361, 74th Cong., 1st Sess. 3 (1935).

[55] *See, e.g.*, Rhone-Poulenc Rorer Pharm., Inc. v. Marion Merrell Dow, Inc., 93 F.3d 511, 514 n.3 (8th Cir. 1996); Bristol-Myers Squibb Co. v. Shalala, 91 F.3d 1493, 1496 (D.C. Cir. 1996); Ortho Pharm. Corp. v. Cosprophar, Inc., 32 F.3d 690, 692 (2d Cir. 1994); Weaver v. Reagen, 886 F.2d 194, 198 (8th Cir. 1989); United States v. An Article of Device . . . Diapulse, 768 F.2d 826, 832 (7th Cir. 1985); Schlessing v. United States, 239 F.2d 885, 886 (9th Cir. 1956); *Washington Legal Found.*, 880 F. Supp. at 28 n.1; United States v. Evers, 453 F. Supp. 1141, 1149-50 (M.D. Ala. 1978), *aff'd*, 643 F.2d 1043, 1052-53 (5th Cir. 1981); FTC v. Simeon Management Corp., 391 F. Supp. 697, 706 (N.D. Cal. 1975), *aff'd*, 532 F.2d 708 (9th Cir. 1976); Upjohn Co. v. MacMurdo, 562 So. 2d 680, 683 (Fla. 1990); Jones v. Petland Orlando Store, 622 So. 2d 1114, 1115 (Fla. Dist. Ct. App. 1993); Haynes v. Baton Rouge Gen. Hosp., 298 So. 2d 149, 153 (La. Ct. App. 1974), *writ denied*, 302 So. 2d 33 (La. 1974); Peter Hutt, *Regulation of the Practice of Medicine Under the Pure Food & Drug Laws*, 33 ASS'N FOOD & DRUG OFFICIALS Q. BULL. 7-11 (1969).

[56] *See, e.g.*, ALA. CODE §§ 27-1-10.1(a), (c) (Supp. 1997) (Alabama); CAL. INS. CODE § 10123.195(a) (West Supp. 1997) (California); CAL. HEALTH & SAFETY CODE § 1367.21(a) (West Supp. 1997) (California); CONN. GEN. STAT. §§ 38a-492b(a), 38a-518b(a) (1995) (Connecticut); FLA. STAT. ANN. § 627.4239 (West 1996) (Florida); GA. CODE ANN. § 33-53-2 (Michie 1993 & Supp. 1997) (Georgia); 1992 ILL. LAWS 980 §§ 1-2 (1992, uncodified) (available on LEXIS, 1992 Ill. ALS 980) (Illinois); 5 ILL. COMP. STAT. § 375/6.4 (West 1993 & Supp. 1997) (Illinois); 215 ILL. COMP. STAT. §§ 5/370r, 125/4-6.3 (West 1993 & Supp. 1997) Illinois); IND. CODE ANN. § 27-8-20-7 (Burns 1993 & Supp. 1997) (Indiana); LA. REV. STAT. ANN. § 22:215.18 (West) (Louisiana);

insurers to pay "for treatments other than those stated in the labeling approved by the FDA."[57] The New Jersey legislature found that off-label use "is legal when prescribed in a medically appropriate way," "conform[s] to the way in which appropriate medical treatment is provided," and is often "necessary and appropriate treatment."[58]

FDA itself recognizes the value and propriety of off-label use. In 1982, the *FDA Drug Bulletin* informed the medical community that "once a [drug] 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."[59] The agency went on to state that

> "unapproved" or more precisely "unlabeled" uses may be appropriate and rational in certain circumstances, and may, in fact reflect approaches to drug therapy that have been extensively reported in medical literature . . . . Valid new uses for drugs already on the market are often first discovered through serendipitous observations and therapeutic innovations . . . .[60]

The policy set forth in that *Drug Bulletin* has been reaffirmed by the agency on numerous occasions.[61] In 1993, responding to questions regarding off-label use of certain bone screws, FDA stated that

> [i]n practice, surgeons often use orthopedic screws which FDA has cleared for other purposes . . . as pedicle screws. Such use of medical devices for non-approved purposes has traditionally been regulated by the hospitals in which the physicians practice and not by the FDA.[62]

In a letter to Joseph Barton, Chairman of the Subcommittee on Oversight and Investigation of the House Committee on Commerce, FDA recently reiterated to Congress that the agency does not regulate the practice of medicine.

MD. CODE ANN., INS., § 15-804 (1997) (Maryland); MASS. GEN. LAWS ANN. ch. 175 §§ 47K-L, 47O-P; ch. 176A §§ 8N, 8Q; ch. 176G § 4G (West Supp. 1996) (Massachusetts); MICH. COMP. LAWS ANN. §§ 500.3406e, 500.3616a (West 1996) (Michigan); N.C. GEN. STAT. §§ 58-67-78, 58-51-59 (Supp. 1996) (North Carolina); N.D. CENT. CODE § 26.1-36-06.1 (1997) (North Dakota); OHIO REV. CODE ANN. § 1751.66 (Banks-Baldwin 1997) (Ohio); OKLA. STAT. ANN. tit. 63 §§ 1-2604, 1-2605 (West 1996) (Oklahoma); R.I. GEN. LAWS §§ 27-55-2, 27-55-3 (1996) (Rhode Island); S.C. CODE ANN. § 38-71-275 (Law. Co-op. 1996) (South Carolina); TENN. CODE ANN. § 56-7-2352 (1997) (Tennessee); UTAH CODE ANN. § 26-18-105(7) (Supp. 1997) (Utah); VA. CODE ANN. § 38.2-3407.5 (Michie 1997) (Virginia).

[57] N.J. STAT. ANN. § 26:1A-36.9(c) (West Supp. 1997) (New Jersey).

[58] *Id.* § 26:1A-36.9(d), (e).

"Off-label" use of FDA-approved drugs provides efficacious drugs at a lower cost. To require that all appropriate uses of a drug undergo approval by the FDA may substantially increase the cost of drugs and delay or even deny patients' ability to obtain medically effective treatment. FDA approval for each use would require substantial expenditure and time to undergo the clinical trials necessary to obtain FDA approval.

Id. § 26:1A-36.9(g).

[59] 12 FDA Drug Bulletin 4-5 (1982) (cited in 59 Fed. Reg. 59,820, 59,821 (Nov. 18, 1994)).

[60] *Id.*

[61] 59 Fed. Reg. at 59,821. *Accord, e.g.*, 52 Fed. Reg. 8798, 8803 (Mar. 19, 1987) (reaffirming legality of off-label use); 48 Fed. Reg. 26,720, 26,733 (June 9, 1983) (reaffirming legality of off-label use); 40 Fed. Reg. 15,392, 15,393-94 (Apr. 7, 1975) (reaffirming legality of off-label use); 37 Fed. Reg. 16,503, 16,503-04 (Aug. 15, 1972) ("[o]nce [an approved] new drug is in a local pharmacy . . . the physician may, as part of the practice of medicine, lawfully . . . vary the conditions of use from those approved"); FOOD AND DRUG ADMIN., COMPLIANCE PROGRAM GUIDANCE MANUAL No. 7382.900 pt. I, at 7 (1992) ("physicians may use devices for off-label uses (This is considered within the practice of medicine)").

[62] FOOD AND DRUG ADMIN., UPDATE ON PEDICLE SCREWS (1993).

> The FD&CA does not reference the practice of medicine and FDA does not view its mission to include regulation of the practice of medicine. FDA's responsibility is the market introduction of new medical products for particular uses . . . . [I]n 1982, the agency issued a policy statement on the "Use of Approved Drugs for Unlabeled Indications," in the FDA Drug Bulletin, which stated that the FD&C Act does not limit the manner in which a physician may use an approved drug in his or her practice.
>
> The Medical Device Amendments (MDA) to the Act give FDA authority to regulate the unapproved use of medical devices. The agency's actions, however, have been the same across product lines because both the statute and the agency's regulations provide for specific exemptions from the Act when the use of a device is part of the practice of medicine.[63]

In this same statement, FDA also stated that it does not regulate off-label use.

> In 1982, the agency issued a policy statement on the "Use of Approved Drugs for Unlabeled Indications," in the FDA Drug Bulletin. That statement reads, in pertinent part:
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> > The FD&C Act does not, however, 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.
>
> The FD&CA provides FDA with explicit regulatory authority over the use of devices. The agency's implementation has been the same, however, because both the statute and the agency's regulations provide exemptions for the use of devices when a part of the practice of medicine.[64]

In response to the suggestions in this letter that FDA had power to interfere with the off-label use of devices, Congress enacted section 214 of the FDAMA, explicitly prohibiting any such FDA intrusion into medical practice with respect to off-label use of devices. FDAMA amends the Act to state that "[n]othing in this 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."[65]

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[63] Attachment to letter from FDA to Hon. Joseph Barton, Chairman, Subcomm. on Oversight and Investigation, House Comm. on Commerce (Apr. 14, 1995) (citations omitted).

[64] *Id.* (citations omitted). More recently, an FDA Deputy Commissioner testified

> The history of the FDC Act indicates that Congress did not intend FDA to interfere with the practice of medicine. Thus, once a product is approved for marketing for a specific use, FDA generally does not regulate how, or for what uses, physicians prescribe [it]. A licensed physician may prescribe a drug for other uses, or in treatments, regimens, or patient populations, that are not listed in the FDA-approved labeling.

Michael Friedman, Deputy Comm'r for Operations, FDA, Prepared Statement Before Subcomm. on Human Resources and Intergovernmental Relations of the House Comm. on Gov't Reform and Oversight (Sept. 12, 1996) (available in 1996 WL 10830744, at *4). *See also* William B. Schultz, Deputy Comm'r for Policy, FDA, Prepared Statement before Senate Comm. on Labor and Human Resources, *available in* S. HRG. 104-445, at 81 (Feb. 22, 1996). Most recently, the FDA stated in a legal brief that "there is a well-established and long-standing FDA policy to refrain from initiating enforcement action against physicians who precribe medical products for unapproved uses." [FDA] Memorandum of Points and Authorities in Opposition to Plaintiff's Motion for Summary Judgment at 13, Washington Legal Found. v. Kessler, C.A. No. 94-1306-RCL (filed Dec. 24, 1997).

[65] Pub. L. No. 105-115, § 214, 111 Stat. at 2348 (codified at 21 U.S.C. § 396 (FDCA § 906)).

Off-label use is not only legal and ethical, but is a common and integral feature of medical practice.[66] The pace of medical discovery invariably runs far ahead of FDA's regulatory machinery, and off-label use is frequently "state-of-the-art treatment."[67]

> New uses for drugs are often discovered after FDA approves the package inserts that explain a drug's approved uses. Congress would have created havoc in the practice of medicine had it required physicians to follow the expensive and time-consuming procedure of obtaining FDA approval before putting drugs to new uses. Thus Congress exempted the practice of medicine from the [FDCA] so as not to limit a physician's ability to treat his patients.[68]

Thus, undue restrictions on off-label use would have adverse health consequences. FDA understands this, and has acknowledged the importance of off-label use at FDLI meetings[69] and elsewhere.[70] The medical community also has emphasized the need for off-label use.[71] For example, the editor of the *Journal of the American Medical Association* testified before Congress that

> [p]rescribing FDA-approved drugs for off-label (unlabeled) uses often is necessary for optimal patient care. For a product to have the most effective potential benefits, law and regulation should and must follow, not precede, science. There are too many variations in clinical circumstances and too much time delay in regulations to allow the government to impede the physician's ability to practice in these regards when it is medically appropriate.[72]

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[66] *See, e.g.*, John Calfee, *Free Speech, FDA Regulation, and Market Effects on the Pharmaceutical Industry*, *in* BAD PRESCRIPTION FOR THE FIRST AMENDMENT: FDA CENSORSHIP OF DRUG ADVERTISING AND PROMOTION 64 (R. Kaplar, ed. 1993) (off-label uses "may come to dominate the original uses for which the drug was approved").

[67] GENERAL ACCOUNTING OFFICE, REPORT TO THE CHAIRMAN, COMM. ON LABOR AND HUMAN RESOURCES, U.S. SENATE, OFF-LABEL DRUGS: REIMBURSEMENT POLICIES CONSTRAIN PHYSICIANS IN THEIR CHOICE OF CANCER THERAPIES 11 (1991) [hereinafter GAO REPORT]. *See also* Christopher, *supra* note 2, at 261 (FDA "could not review drugs in its lengthy testing process at a pace equal to that at which physicians discover beneficial off-label uses").

[68] United States v. Algon Chemical, Inc., 879 F.2d 1154, 1163 (3d Cir. 1989) (quoting Chaney v. Heckler, 718 F.2d 1174, 1180 (D.C. Cir. 1983), *rev'd on other grounds*, 470 U.S. 821 (1985)).

[69] On February 26, 1992, then-FDA Deputy Commissioner for Policy, Michael Taylor, stated in a speech to FDLI that off-label uses are "often essential to good medical practice, and in some areas . . . constitute a significant portion of standard therapy." Richard Kaplar, *Conclusion: Valuing the Freedom of Speech*, *in* BAD PRESCRIPTION FOR THE FIRST AMENDMENT, *supra* note 66, at 111.

[70] Valid new uses for drugs already on the market are often first discovered through serendipitous observations and therapeutic innovations, subsequently confirmed by well-planned and executed clinical investigations. Before such advances can be added to the approved labeling, however, data substantiating the effectiveness of a new use or regimen must be submitted by the manufacturer to FDA for evaluation. This may take time and, without the initiative of the drug manufacturer whose product is involved, may never occur. For that reason, accepted medical practice often includes drug use that is not reflected in approved drug labeling.

FDA DRUG BULLETIN, *supra* note 59, at 4, 5.

[71] *See, e.g.*, Ian Gilron, *The Introduction of New Drugs Into Anaesthetic Practice: A Perspective in Pharmaceutical Development and Regulation*, 42 CAN. J. ANAESTHESIA 516, 519 (1995) ("[U]napproved drug uses often become the mainstay of clinical practice without being legally approved.") (discussing five major off-label uses in anaesthesia); Kathleen Kerr, *New Heart Cases Spur Fen-Phen Label Move*, NEWSDAY, Aug. 28, 1997, at A52 ("it is legal and quite common for doctors to prescribe an 'off-label' use of drugs for other than FDA-approved purposes").

[72] *Promotion of Drugs and Medical Devices for Unapproved Uses: Hearing Before the Human Resources and Intergovernmental Relations Subcomm. of the House Comm. on Gov't Operations*, 102d Cong., 1st Sess. 103 (1991) (statement of George Lundberg, M.D.).

Off-label uses of medical devices and drugs perform an important therapeutic role in many, if not most, areas of medical practice. Prescriptions for off-label uses of drug products "may account for more than 25% of the approximately 1.6 billion prescriptions written each year, with some recent estimates running as high as 60%."[73] Examples of medical conditions whose standard treatments involve or have involved extensive off-label use include cancer,[74] heart and circulatory disease,[75] AIDS,[76] kidney diseases requiring dialysis,[77] osteoporosis,[78] spinal fusion surgery,[79] and various uncommon diseases.[80] Pediatric uses also are mostly off-label.[81] Thus, "[i]n some cases, if you didn't use the drug in the off-label way, you'd be guilty of malpractice."[82]

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[73] Lars A. Noah, *Constraints on Off-Label Uses*, 16(2) J. PROD. & TOXICS LIAB. 139, 139 (1994) (footnotes omitted). *See* Fran Kritz, *FDA Seeks to Add Drugs' Uses to Labels*, WASH. POST, Mar. 29, 1997, at 11 (citing American Medical Association estimate of 40% to 60%).

[74] "Off-label drug use is common, and even predominant, in the treatment of cancer patients." GAO REPORT, *supra* note 67, at 40 (conclusions); *id.* at 13-14 (65% of all anticancer drug use is off-label). Off-label cancer treatments total about $100,000,000 annually. *Firms Tread Path to Favorable Off-Label Use Reimbursement*, FOOD & DRUG LETTER, June 4, 1993.

[75] Gregory Mundy et al., *Current Medical Practice & The Food & Drug Administration*, 229 JAMA 1744, 1746 (1974) (describing prevalence of off-label use in treating angina and hypertension). The off-label use of beta-blockers following heart attacks has "proved of immense value." *FDA Seeking Prioritized List of Off-Label Uses Deemed Most Important by 10 Professional Societies*, 5 HEALTH NEWS DAILY 4 (May 6, 1993) (quoting letter from FDA).

[76] More than 80% of AIDS patients are treated with at least one drug being prescribed off-label, and more than 40% of all drugs prescribed for AIDS treatment are prescribed off-label. Carol Brosgart et al., *Off-Label Use in Human Immunodeficiency Virus Disease*, 12 J. ACQUIRED IMMUNE DEFICIENCY SYNDROMES & HUMAN RETROVIROLOGY 56, 57-58 (1996).

[77] Some 70% of kidney dialysis patients use their dialysis equipment in an off-label manner. *FDA and Dialyzer Makers Spar Over Device Reuse*, FOOD & DRUG LETTER, Apr. 8, 1994.

[78] F-D-C REP. ("The Pink Sheet"), Dec. 20, 1993, at T&G-4 (describing treatments for osteoporosis as the most commonly mentioned off-label use reported by manufacturers to FDA); *Doctor's Page: Antiresorptive Therapy for Men*, OSTEOPOROSIS ONLINE FROM SOUTHEAST TEXAS (visited Oct. 1, 1997) <http://www.ih2000.net/osteoporosis/MenRX.htm> ("No drugs are currently approved by the FDA for treatment of men with osteoporosis. However currently available [drugs] are reasonable to consider as off-label therapeutic interventions.").

[79] Off-label use of bone screws occurs "in a large portion of the 30,000 to 70,000 spinal stabilization procedures performed annually." *Pedicle Screws*, 21 FDA MED. BULL. 10 (1994). *See, e.g.*, AMERICAN ACADEMY OF ORTHOPEDIC SURGEONS, POSITION PAPER (Oct. 27, 1993) ("surgery utilizing pedicle screws represents the best available treatment for patients").

[80] Most diseases afflicting fewer than 200,000 Americans are "totally without" FDA-labeled treatment. Some "90 percent of [patients] must rely on 'off-label' uses" to have any treatment at all. Abbey S. Meyers, Pres., National Org. for Rare Diseases, Inc., Prepared Testimony Before Subcomm. on Human Resources and Intergovernmental Relations of the House Comm. on Gov't Reform and Oversight (Sept. 12, 1996). For a general discussion of other off-label uses, see Katie Rodgers, *Dealing with Incontinence*, 140 DRUG TOPICS 114 (1996) (six of seven treatments for urinary incontinence in guidelines of Agency for Health Care Policy & Research are off-label uses); Doug Podolsky, *Doing Double Duty*, U.S. NEWS & WORLD REP., June 26, 1995, at 62-63 (listing six common off-label uses of drugs); Richard Palmer & Shanthi Gaur, *Off-Label Use of Prescription Drugs & Devices*, RX FOR DEF., Spring 1995, at 4, 5 (listing five common off-label uses of drugs and three common off-label uses of medical devices); Ricahrd Samp & Alan Slobodin, *FDA Censorship Threatens Patient Medical Care*, 77 CONSUMER'S RES. MAG. 16 (1994) (listing "medically accepted" off-label uses for 28 common drugs); *Some Drugs' Unapproved Uses Bring Results*, CHARLESTON GAZETTE, Oct. 31, 1994, at 3B (listing 10 "double-duty drugs" with common off-label uses); S. Carrell, *Unapproved Uses for Drugs Decrease with Time on Market*, 137 DRUG TOPICS 44 (1993) (looking at the 22 most-prescribed drugs in 1989, off-label prescriptions totaled more than 50% for 6 drugs and more than 20% for 11 drugs); *Cosprophar*, 32 F.3d at 692 (45% of sales of Retin-A, a drug approved for acne, are for off-label treatment of aged skin).

[81] "[O]ver 80% of all drugs prescribed for children carry . . . orphaning clauses in their package labels." ROBERT LEVINE, ETHICS AND REGULATION OF CLINICAL RESEARCH 241 (2d ed. 1986). "Orphaning clauses" are disclaimers with respect to pediatric use that FDA requires because of the paucity of clinical studies involving children. *Id.* at 239.

[82] Kritz, *supra* note 73 (quoting American Medical Association vice-president).

[83] Ronald Munson, *Intervention and Reflection: Basic Issues in Medical Ethics*, *in* MEDICAL EXPERIMEN-

B. *Off-Label Use is Neither "Research" Nor "Experimental"*

The mere fact that a product is used off-label to treat a patient does not make that use research. As a matter of medical ethics, there is a distinction between the "practice of medicine" and "research."

> Medical therapy aims at relieving the suffering of people and restoring them to health. It attempts to cure diseases, correct disorders, and bring about normal bodily functioning. Its focus is on the individual patient, and his or her welfare is its primary concern.
>
> Medical research, by contrast, is a scientific enterprise. Its aim is to acquire a better understanding of the chemical and physiological processes that are involved in human functioning. It is concerned with the effectiveness of therapies in ending disease . . . . But this concern is not for the patient as an individual. Rather it is directed toward establishing theories. The hope, of course, is that this theoretical understanding can be used as a basis for treating individuals. But helping a particular patient get well is not a goal of medical research.[83]

Thus, when devices and drugs are used off-label as part of the practice of medicine, "[t]he primary purpose . . . is to benefit the individual patient."[84] These distinctions were explained by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in its 1978 *Belmont Report*, prepared for the President of the United States.

> It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other . . . .
>
> For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or

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TATION & INFORMED CONSENT 324 (4th ed. 1992). The two concepts were defined and contrasted in Robert Levine's work.

> The term "research" refers to a class of activities designed to develop or contribute to generalizable knowledge. Generalizable knowledge consists of theories, principles or relationships (or the accumulation of data on which they may be based) that can be corroborated by accepted scientific observation and inference.
>
> The "practice" of medicine . . . refers to a class of activities designed solely to enhance the well-being of an individual patient or client. The purpose of medical . . . practice is to provide diagnosis, preventive treatment, or therapy. The customary standard for routine and accepted practice is a reasonable expectation of success. The absence of validation or precision on which to base such an expectation, however, does not in and of itself define the activity in question as research. Uncertainty is inherent in therapeutic practice because of the variability of the physiological and behavioral responses of humans. This kind of uncertainty is, itself, routine and accepted.

LEVINE, *supra* note 81, at 3. *See also* George J. Annas, *Questing for Holy Grails: Duplicity, Betrayal and Self-Deception in Postmodern Medical Research*, 12 J. CONTEMP. HEALTH L. & POL'Y 297, 323 (1996) ("Research is research, designed to test a hypothesis and performed based on the rules of the protocol; treatment is something else, designed to benefit a patient, and subject to change whenever change is seen in the patient's best interest"); TOM BEAUCHAMP & JAMES CHILDRESS, PRINCIPLES OF BIOMEDICAL ETHICS 441 (4th ed. 1994); William F. Rayburn, *A Physician's Prerogative to Prescribe Drugs for Off-Label Uses During Pregnancy*, 81 J. OBSTETRICS & GYNECOLOGY 1054 (1993) ("[d]eparture from formally approved prescribing standards occurs commonly, and does not, in and of itself, constitute research").

[84] AMERICAN COLLEGE OF PHYSICIANS, ETHICS MANUAL 959 (3d ed. 1992) (reprinted from 117 ANNALS INTERNAL MED. 97 (1992)).

> behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. By contrast, the term "research" designates an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge . . . . Research is usually described in a formal protocol that sets forth an objective and a set of procedures to reach that objective.[85]

Nor does a physician's use of medical devices or drugs off-label convert them into experimental or investigational products.[86] "[A] treatment found to be in accordance with generally accepted standards of medical practice would hardly be experimental."[87] As one leading medical ethicist explained, "[m]any drugs and devices approved for use by the FDA are prescribed for uses that are not listed on the FDA-approved package label. This does not mean that all such uses must be made the object of a formal study designed to establish safety and efficacy."[88]

Because FDA premarket review of drugs and medical devices involves extensive scrutiny, the agency ordinarily has reasonable assurance that marketed products are safe, both for their labeled uses and for general use.[89] As the fen/phen example indicates, previously unknown safety concerns can arise with labeled as well as unlabeled indications. When FDA makes decisions that allow drugs and medical devices to be marketed, the agency is well aware that these products likely are to be put to off-label use. Indeed, the agency has stated that

> [g]ood medical practice and patient interests require that physicians use commercially available drugs, devices, and biologics according to their best knowledge and judgment . . . . Use of a product in this manner as part of the "practice of medicine" does not require the submission of an Investigational New Drug Application (IND) or an Investigational Device Exemption (IDE),

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[85] NATIONAL COMM'N FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, BELMONT REPORT 2-3 (1978). *See also* Kathryn Tuthill, *Human Experimentation: Protecting Patient Autonomy Through Informed Consent*, 18 J. LEGAL MED. 221, 222-24 (1997) (applying *Belmont Report* standard). Federal regulations define "research" as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge." 45 C.F.R. § 46.102(d) (1997). Subpart A of chapter 45 is the "Basic HHS Policy for Protection of Human Research Subjects" and it "applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency." *Id.* § 46.101(a).

[86] "Experimental" is defined at title 21 of the *Code of Federal Regulations* section 312.3(b) (discussing clinical investigation) and section 50.3(c) (discussing IND informed consent); the term "investigational" is defined at section 812.3(h) (IDE devices). IDE devices are not necessarily (or even usually) experimental. FDA categorizes IDE devices as either experimental or nonexperimental investigational; the nonexperimental category of IDE devices are those that FDA "believe[s] to be in Class I or Class II, or a device believed to be in Class III for which . . . underlying questions of safety and effectiveness . . . have been resolved." 61 Fed. Reg. 7011, 7011-12 (Feb. 23, 1996). Medical treatment using nonexperimental IDE devices is reimbursed by Medicare. *Id.; see* 42 C.F.R § 405.205 (1997).

[87] Pirozzi v. Blue Cross-Blue Shield, 741 F. Supp. 586, 590 (E.D. Va. 1990) (quotation marks omitted). *See also Weaver*, 886 F.2d at 198 (experimental treatment is "not generally accepted by the professional medical community as an effective and proven treatment for the condition" or is "rarely used, novel or relatively unknown").

[88] LEVINE, *supra* note 81.

[89] Even in the less demanding 510(k) notification process, detailed information is required of the manufacturer and is considered by FDA. *See supra* text accompanying notes 8-22.

[90] FOOD AND DRUG ADMIN., INVESTIGATIONAL USE OF MARKETED PRODUCTS (1989). "[I]t is not the agency's [FDA's] policy, intent, or bias to indicate that off-label uses are wrong, improper or even investigational." GAO REPORT, *supra* note 67, at 11. *Cf.* Duvall v. Bristol-Myers-Squibb Co., 103 F.3d 324, 330 (4th Cir. 1996) (IDE regulations apply only to devices actually used in the IDE).

> or review by an IRB, unless such review is required by the institution in which the product will be used.
>
> The investigational use of an approved, marketed products differs from the situation described above. "Investigational use" suggests the use of an approved product in the context of a study protocol . . . .
>
> The investigational use of an approved marketed device requires the submission of an IDE when the principal intent of the investigational use is to develop information about the device's safety and efficacy for uses other than which it was approved.[90]

Thus, FDA itself recognizes that the off-label use of medical devices and drugs by physicians engaged in the practice of medicine differs from the investigational use of such products. Indeed, its regulations provide that investigational new drug requirements "do[] not apply to the use in the practice of medicine for an unlabeled indication."[91]

Accordingly, the consensus position is that off-label use of medical devices and drugs by physicians seeking the optimal treatment for their patients is not equivalent to research, investigational, or experimental treatment. "The mere fact of a departure from the manufacturer's recommendation where such departure is customarily followed by physicians . . . does not make that departure an 'experiment.' There was in this case no evidence of experiment and the instructions concerning 'experiment' should not have been given."[92] "Off-label" is merely a regulatory description of the use of a medical device or drug — a legal status, not a medical fact.[93] A product's regulatory status can change over time.[94] If FDA were to allow a labeling change for a drug or medical device that added a use that is currently off-label, that regulatory decision would not make any patient's treatment more likely to succeed; nor would it reduce the risk of any complication. "[T]he status of the drug with the FDA does not alter the relationship between drug manufacturer, physician and patient."[95]

Unfortunately, terminology problems persist. It is common parlance to say that a drug or device is FDA "approved" for a given use if that use appears on the label.[96]

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[91] 21 C.F.R. § 312.2(d).

[92] Ramon v. Farr, 770 P.2d 131, 135 (Utah 1989) (emphasis original) (*quoting* Salgo v. Leland Stanford, Jr. University Board of Trustees, 317 P.2d 170, 180 (Cal. Ct. App. 1957)). *See Weaver*, 886 F.2d at 198-99 (rejecting as "overly broad" a claim that all drug use "outside the FDA approved indications is per se 'experimental'"); Doe v. Sullivan, 756 F. Supp. 12, 15-16 (D.D.C.) ("[U]se of unapproved drugs does not involve the type of scientific investigation under controlled circumstances that "research" connotes . . . . The FDA, therefore, does not view every use of unapproved drugs as research.") (citation omitted), *aff'd*, 938 F.2d 1370 (D.C. Cir. 1991); *Simeon Management Corp.*, 391 F. Supp. at 706; *Femrite*, 568 N.W.2d at 540-41 (patient treated off-label with same device in same way as in an IDE was not subjected to "experimental research" or "investigational study"); Wyttenhove v. Fairview Hosp. & Healthcare Serv., No. MP 95-14941 (Minn. Dist. Hennepin Co. Sept. 24, 1996) (off-label use held not to be "experimental"), *aff'd mem.*, No. C3-97-51, 1997 WL 585813 (Minn. App. Sept. 23, 1997).

[93] FDA regulatory status is not a "risk" of surgery. *Klein*, 673 N.E.2d at 231.

[94] *See generally* 21 C.F.R §§ 312.34 (providing for use of investigational drugs as treatment outside of IND), 314.70 - 314.71 (procedures for changing approved applications of drugs), pt. 860, subpt. C (procedures for reclassification of medical devices).

[95] Tracey v. Merrell Dow Pharmaceuticals, 569 N.E.2d 875, 880 (Ohio 1991). The same is true for medical devices. *See Orthopedic Bone Screw*, 1996 WL 107556, at *3 ("FDA labels given to a medical device do not speak directly to the medical issues surrounding a particular surgery. They are not, therefore, required to be disclosed pursuant to the law of informed consent.").

[96] This description formerly might violate even FDA regulations. For example, 510(k) medical devices are not "approved" at all, and their manufacturers are forbidden from claiming that they are. 21 C.F.R. § 807.97. This regulation is now questionable, however, because its statutory basis, 21 U.S.C. § 331(l), was repealed by section 421 of the FDAMA. Pub. L. No. 105-115, § 421, 111 Stat. at 2380.

The converse proposition, however, (which is decidedly not true) would be that such products are "unapproved" for all unlabeled uses. This erroneous concept of unapproved use takes on derogatory connotations if divorced from a regulatory context, as would be the case in an informed consent discussion. To those unfamiliar with FDA regulation, a group that includes most patients, unapproved suggests "*dis*approved" — that is, some affirmative determination by FDA that an off-label use is actually unsafe or too risky to appear on labeling.[97] FDA ordinarily looks to a manufacturer's intended uses when considering how a drug or device is to be marketed and labeled.[98] Thus, absent a labeled contraindication, unindicated uses cannot be considered unapproved; they simply have not been reviewed at all.[99]

Nor can it be assumed that off-label uses are unproven or unsafe because they have escaped FDA scrutiny. Nothing in the FDCA or the conforming regulations suggests that FDA is to conduct its own evaluations of uses other than those proposed by a manufacturer.[100] At least with respect to devices, however, it appears that in some cases actual FDA practice has been otherwise. A congressional investigation into FDA procedures revealed that, "[o]ver the years, FDA has made premarket regulatory decisions based on uses for devices that are unrelated to the intended uses set forth in labeling."[101] FDA's practice of informally reviewing uses other than those to be included on labeling invalidates any assumption that, simply because a use does not appear on FDA labeling, a use has received no regulatory review. Whether or not FDA, in fact, has examined any particular off-label use thus would require detailed review of product-specific regulatory history, which is something that physicians would be ill-equipped to undertake.[102]

Thus, it is not possible to draw any conclusion about the safety or effectiveness of a particular use of a drug or medical device from the administrative/legal status of that use as off-label.[103] In many, if not most, cases, FDA will have made no determination,

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[97] "Off-label drug use by oncologists is quite common" but people "mistakenly equate[] the off-label categorization of these uses . . . with lack of evidence of effectiveness." *Letter to the Editor*, 267 JAMA 2473-74 (1992). A recent notable example of a court falling into precisely this error is Proctor v. Davis, 682 N.E.2d 1203, 1213 (Ill. App. 1997), in which the court repeatedly refers to off-label use as "unauthorized" by FDA, when, as previously discussed, the agency lacks and has disclaimed any power to allow or disallow off-label use.

[98] *See* 21 U.S.C. § 360e(d) (FDA "shall rely on the conditions of use included in the proposed labeling as the basis for determining whether or not there is a reasonable assurance of safety and effectiveness" for purpose of PMAs); 21 C.F.R. §§ 314.50(a)(1) (proposed indications to be stated in IND), 314.54 (amending INDs to add indications), 807.100(b)(1) (FDA action based upon intended use in premarket notification), 807.92(a)(5) (describing required manufacturer statement of intended use).

[99] This appears to be the situation in the *Proctor* case. In *Proctor*, no application was filed with FDA concerning the off-label use at issue. 682 N.E.2d at 1209-10. Indeed, FDA refused the manufacturer's request to add adverse reactions relating to that precise off-label use to its labeling shortly before the incident at suit. *Id.* at 1210. For unexplained reasons the manufacturer's request, and FDA's refusal of it, were excluded from evidence in *Proctor*, *id.*, and the court took the position that the manufacturer was liable for not including in its labeling the information that FDA had refused to allow. *Id.* at 1214.

[100] *See* Guidance on the Center for Devices and Radiological Health's Premarket Notification Review Program, FDA Guidance Doc. No. K86-3, at 7 (June 30, 1986) ("if a device has a different intended use, there is no reason to proceed further to decide whether the devices are substantially equivalent"). The FDAMA recently gave FDA the right, for a five-year trial period, to consider off-label uses in its 510(k) review process and to require appropriate labeling changes. Pub. L. No. 105-115, § 205(b), 111 Stat. at 2337-38 (codified at 21 U.S.C. § 360c(i)(1)(E)).

[101] *See* S. REP. No. 105-43, 105th Cong., 1st Sess. 27 (1997).

[102] *See infra* text accompanying notes 228-231.

[103] The reason for the omission of a use from FDA-regulated labeling could be any of the following: 1) FDA lacked sufficient information to make an affirmative finding of safety or effectiveness; 2) the manufacturer never submitted an application concerning the use to FDA; or 3) in the case of a device, FDA lacked evidence of a substantially equivalent predicate (pre-1976) device.

affirmative or negative, about any given off-label use. The only certain conclusion is that FDA considers the product generally safe enough to be on the market.[104]

"Off-label" thus only means "silent" label.[105] The term denotes nothing about health risks or benefits, and therefore means nothing in the medical context of informed consent. Even if "off-label" connoted more than legal status, it is (without more) medically neutral. One cannot generalize about risks of off-label use because these uses run the "gamut from 'clearly experimental use to standard therapy and even to state of the art treatment.'"[106] To the extent that lay patients equate "unapproved" with "disapproved," reference to off-label status would be harmful, in that it could induce patients to refuse widely accepted off-label therapies.[107]

IV. FEDERAL INFORMED CONSENT OBLIGATIONS FOR IDEs OR INDs DO NOT APPLY TO OFF-LABEL USE

Describing off-label uses as investigational based on the mere fact that a label is silent is an inaccurate conclusion. In the legal context of informed consent litigation, the potential for confusion is compounded because this description also misuses FDA terminology with precise regulatory meaning. There are particularized informed consent regulations governing investigational drugs and devices, but these regulations do not, and should not, apply to off-label use. FDA never intended off-label use to come under its rubric for investigations.[108]

The text of title 21 of the *Code of Federal Regulations* part 50, relating to the "Protection of Human Subjects," is applicable only to clinical investigations, not off-label use.[109] As discussed above, clinical investigations are clinical trials occurring for medical devices under investigational device exemptions and for investigational new drugs,[110] and research that, under any FDA regulation, is "intended to be submitted later to, or held for inspection by, the [FDA] as part of an application or a research or a marketing permit."[111]

FDA's regulations provide that participation in any IND or IDE clinical trial is voluntary.[112] Participation is expressly contingent on the physician's (investigator's)

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[104] *See supra* text accompanying notes 89-102.

[105] *See supra* note 2. FDA's webpage includes a description of "off-label" as "use for indication, dosage form, dose regimen, population or other use parameter not mentioned in the approved labeling." Janet Woodcock, *Shift in Regulatory Approach*, FDA slide presentation at DIA Montreal 3 (June 23, 1997), *available in* <http://www.fda.gov/cder/present/diamontreal/regappr/sld003.html>

[106] GAO REPORT, *supra* note 67, at 11.

[107] Senator Frist, a physician, asked

> Now what does off-label mean? Off-label scares people. Is somebody going in some secret closet and pulling out a medicine and using it? No . . . that is why "extra label" is probably a better term. But right now off-label is something that we in the medical profession understand is used routinely . . . probably 50 percent of all pediatric drugs prescribed are off-label. So it is not a term to be scared of or to fear.

143 CONG. REC. S8165 (daily ed. July 28, 1997).

[108] The legal and ethical distinctions between "research" and "therapy" made in the *Belmont Report* were recognized by FDA when it promulgated title 21 of the *Code of Federal Regulations* part 50. *See* 44 Fed. Reg. 47,713, 47,716 (Aug. 14, 1979) (referencing *Belmont Report* and other Commission reports).

[109] 21 C.F.R. pt 50.

[110] *See supra* text accompanying notes 26-32, 41-42.

[111] The "intent" language of section 50.3(c) "is intended solely as a shorthand way of referring to at least 22 separate categories of information that are now, or in the near future will become, subject to requirements for submission to the agency." 44 Fed. Reg. at 47,719.

[112] The FDCA contains no provisions that can force physicians or hospitals to participate in an IDE or IND clinical trial against their will. *See* 21 C.F.R. §§ 56.109(a), 312.66, 812.42 (no investigation may begin unless

agreement to abide by FDA's informed consent regulations.[113] A manufacturer sponsoring an IND or IDE clinical trial cannot obtain FDA approval of the trial until it obtains written commitments or agreements signed by each physician participating in the trial.[114] Physicians engaged in clinical trials as investigators voluntarily agree to FDA informed consent standards beyond the duties recognized by the common law. They accept these extra obligations in return for the benefits of participation in FDA-approved medical research.[115] In contrast, there is no express voluntary undertaking and no benefit to the physician in the more common case, when he or she simply is treating a patient with a product in a way about which the label is silent — when only off-label use, not FDA investigational use, is at issue.[116]

Federal requirements exceeding the common law can result in civil liability only when a physician voluntarily assumes such requirements.[117] Neither the language of part 50, nor FDA's contemporaneous explanation of it, indicates that the agency ever intended for part 50 to apply to the off-label use of medical devices or drugs by physicians practicing medicine. The recently enacted statutory prohibition on FDA interference with the practice of medicine is evidence that Congress agrees with this limitation.[118]

V. STATE INFORMED CONSENT LAWS REQUIRE DISCUSSION ONLY OF THE NATURE, RISKS, BENEFITS, AND ALTERNATIVES OF MEDICAL PROCEDURES

Although many aspects of the fifty states' doctrines of informed consent vary, they uniformly restrict the information that physicians are required to explain about medical risks, medical benefits, the nature of the treatment, and the medical condition(s) that the treatment is intended to remedy.[119] Many states also require discussion of alternative modes of treatment.[120] Actions for informed consent thus are limited to the nondisclosure of medical information. There is a "therapeutic limitation inherent in the doctrine of informed consent."[121]

Patients sometimes assert that they should have been told information that is not relevant to medical risk, but this does not mean that the informed consent doctrine should be expanded to require disclosure.[122] For example, the plaintiff in *Spencer v.*

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the investigational plan has been approved by an IRB). *Cf.* Friter v. Iolab Corp., 607 A.2d 1111, 1115 (Pa. Super. Ct. 1992) (hospital had informed consent liability going beyond common-law duties only when it voluntarily assumed IDE obligations); Kus v. Sherman Hosp., 644 N.E.2d 1214, 1221 (Ill. App. Ct. 1995) (same), *appeal denied*, 652 N.E.2d 343 (Ill. 1995).

[113] *See* text accompanying notes 39-42, 45-46.

[114] 21 C.F.R. §§ 312.53(c), 812.43(c).

[115] Physicians who perform a medical procedure within the context of a clinical investigation are required, per FDA clinical investigation regulations, to inform the patient-participant of the investigational nature of the medical device. They are required to give the patient-participants such information not because state informed consent law mandates it, but rather in return for the benefit of engaging in a research project that has received the FDA's "stamp" of approval.

Orthopedic Bone Screw, 1996 WL 107556, at *4.

[116] *See id.*

[117] *See, e.g., id.* (discussing *Friter*, 607 A.2d at 1111).

[118] Pub. L. No. 105-115, § 214, 111 Stat. at 2348 (codified at 21 U.S.C. § 396 (FDCA § 906)).

[119] *See infra* text accompanying notes 128-130.

[120] *Id.*

[121] Arato v. Avedon, 858 P.2d 598, 609 (Cal. 1993).

[122] "The fact that a physician has 'fiducial' obligations . . . does not mean that he or she is under a duty, the scope of which is undefined, to disclose every contingency that might affect the patient's *nonmedical* 'rights and interests.'" *Arato*, 858 P.2d at 608-09 (citation and footnote omitted) (emphasis original).

Seikel[123] wanted her physician to inform her that third trimester abortions were legal in adjoining states. The Oklahoma Supreme Court rejected this claim, holding that the doctrine of informed consent "do[es] not impose upon physicians a duty to know or disclose the laws."[124] Assessing the legal status of abortion was "a job more suitable for lawyers."[125] Likewise, although a patient might want to know about it, the possibility of malpractice need not be disclosed, because "unskillful performance . . . is not a 'risk' in the sense of a risk benefit analysis material to a decision on informed consent. The court does not read the law of informed consent to require a physician to raise the possibility . . . that he might perform the operation unskillfully."[126]

More recently, a plaintiff contended that her surgeon was obligated legally to inform her that the medical device he was implanting was being put to an off-label use. The Ohio Court of Appeals rejected her informed consent claim.

> [T]he decision whether to use a drug for an off-label purpose is a matter of medical judgment, not of regulatory approval. By analogy, the off-label use of a medical device is also a matter of medical judgment and, as such, subjects a physician to professional liability for exercising professional medical judgment. Off-label use of a medical device is not a material risk inherently involved in a proposed therapy which a physician should disclose to a patient prior to the therapy. Therefore, since [the defendant physician] engaged in off-label use of this medical device he could be subject to professional liability for medical negligence, but in this case those claims have been litigated and are not before us. Accordingly, we conclude that failure to disclose FDA status does not raise a material issue of fact as to informed consent.[127]

Informed consent responsibility is limited to nondisclosure of relevant medical information. Physicians ordinarily are required to provide patients with information about "the nature of the ailment, the nature of the proposed treatment, the probability of success of the contemplated therapy and its alternatives, and the risk of unfortunate consequences."[128] Some states restrict the informed consent duty to only recognized

[123] 742 P.2d 1126 (Okla. 1987).

[124] *Id.* at 1129.

[125] *Id.*

[126] Aceto v. Dougherty, 615 N.E.2d 188, 191 (Mass. 1993). Likewise, although a patient may want to know how his or her physician performed in a particular medical school class, and might consider it material to a decision to pursue treatment, that information is not material to any particular medical risk.

[127] *Klein*, 673 N.E.2d at 231.

[128] Reed v. Campagnolo, 630 A.2d 1145, 1146 (Md. 1993). *See, e.g.*, Reidisser v. Nelson, 534 P.2d 1052, 1054 (Ariz. 1975) ("all the reasonable and recognized risks" of treatment, as well as "the nature of the surgical procedure attempted and the probable results") (citation and quotation marks omitted); Canterbury v. Spence, 464 F.2d 772, 787-88 (D.C. Cir.) ("hazards of the proposed treatment," "alternatives," and likely results of nontreatment), *cert. denied*, 409 U.S. 1064 (1972); Zalazar v. Vercimak, 633 N.E.2d 1223, 1226 (Ill. App. Ct. 1993) ("risks of surgery," "foreseeable results," and "reasonable alternatives"); Palmer v. Biloxi Reg'l Med. Ctr., 564 So. 2d 1346, 1363 (Miss. 1990) ("diagnosis," "nature and purpose of the treatment," "risks and consequences," "probable success," "alternatives," and "prognosis if the treatment is not administered"); Harrell v. Witt, 755 S.W.2d 296, 299 (Mo. Ct. App. 1988) ("specific risks" and "the existence and feasibility of specific possible alternatives"); Largey v. Rothman, 540 A.2d 504, 506 (N.J. 1988) ("nature of treatment," "substantial risks," and "alternative therapies"); Petriello v. Kalman, 576 A.2d 474, 478 (Conn. 1990) ("nature of the procedure," "risks," "hazards," "alternatives," and "anticipated benefits"); Miller v. Rhode Island Hosp., 625 A.2d 778, 783 (R.I. 1993) ("what [is] to be done, the risk involved and the alternatives to the contemplated treatment") (citation and quotation marks omitted); Hook v. Rothstein, 316 S.E.2d 690, 694-95 (S.C. Ct. App.) ("diagnosis," "general nature of the contemplated procedure," "material risks," "probability of success," "prognosis" if untreated, and "existence of any alternatives"), *cert. denied*, 320 S.E.2d 35 (S.C. 1984); Rizzo v. Schiller, 445 S.E.2d 153, 155 (Va. 1994) ("specific procedures," "foreseeable risks," and "risks of non-treatment").

medical risks.[129]

In many jurisdictions, informed consent requirements are codified.[130] These states similarly limit the scope of required information to medical issues. For example, New York's statute states

> Lack of informed consent means the failure of the person providing the professional treatment or diagnosis to disclose to the patient such alternatives thereto and the reasonably foreseeable risks and benefits involved as a reasonable medical . . . practitioner under similar circumstances would have disclosed, in a manner permitting the patient to make a knowledgeable evaluation.[131]

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[129] *See* Nickell v. Gonzalez, 477 N.E.2d 1145, 1148 (Ohio 1985) ("fail[ure] to disclose to the patient and discuss the material risks and dangers inherently and potentially involved with respect to the proposed therapy"). *See also* Craig v. Borcicky, 557 So. 2d 1253, 1258 (Ala. 1990) ("the significant perils involved in the procedure") (quotation marks omitted); Kerr v. Carlos, 582 N.E.2d 860, 864 (Ind. Ct. App. 1991) ("inherent risks of the proposed treatment"); Kennis v. Mercy Hosp. Med. Ctr., 491 N.W.2d 161, 166 (Iowa 1992) ("material risks"); Cornfeldt v. Tongen, 262 N.W.2d 684, 699-701 (Minn. 1977) (recognizing informed consent as a claim for "negligent nondisclosure" of a "risk").

[130] *See* ALASKA STAT. § 9.55.556 (Michie 1996) ("common risks and reasonable alternatives to the proposed treatment or procedure"); ARK. CODE ANN. § 16-114-206(b) (Michie 1987) ("risks or hazards inherent in such treatment"); DEL. CODE ANN. tit. 18, § 6852 (1997) ("risks of the treatment, procedure or surgery"); FLA. STAT. ANN. § 766.103(3)(a) (West Supp. 1996) ("the medically acceptable alternative procedures or treatments, and the substantial risks and hazards inherent in the proposed treatments or procedures"); GA. CODE ANN. § 31-9-6(d) (1991) ("in general terms [of] the treatment or course of treatment"); HAW. REV. STAT. § 671-3(b) (1985) ("[t]he condition being treated," "[t]he nature and character of the proposed treatment," "anticipated results," "recognized possible alternative forms of treatment," and "recognized serious possible risks, complications, and anticipated benefits involved in the treatment or surgical procedure, and in the recognized possible alternative[s]"); IDAHO CODE § 39-4304 (1993) ("the need for, the nature of and the significant risks ordinarily attendant"); 20 ILL. COMP. STAT. ANN. 301/30-5(p) (West 1997) ("complete and current information concerning the nature of care, procedures, and treatment"); IND. CODE § 27-12-3 (1996) ("general nature of . . . condition," "proposed treatment," "expected outcome," "material risks," and "reasonable alternatives"); IOWA CODE ANN. § 147.137(1) (West 1989) ("in general terms the nature and purpose of the procedure or procedures, together with the known risks . . . , with the probability of each such risk if reasonably determinable"); KY. REV. STAT. ANN. § 304.40-320(2) (Michie 1988) ("a general understanding of the procedure," "acceptable alternative procedures," "substantial risks and hazards"); LA. REV. STAT. ANN. § 40:1299.40 (A), (C) (West 1992) ("in general terms the nature and purpose of the procedure or procedures," together with the existence of enumerated "known" risks); ME. REV. STAT. ANN. tit. 24 § 2905(1)(B) (West 1990) ("a general understanding of the procedure[]," "usual and most frequent risks"); MINN. STAT. ANN. § 144.651 (West 1996) ("information concerning . . . diagnosis, treatment, alternatives, risks and prognosis"); NEB. REV. STAT. § 44-2816 (1996) ("information ordinarily provided . . . [about] operation, treatment or procedure"); NEV. REV. STAT. § 41A.110 (1995) ("in general terms . . . the procedure," "alternative methods of treatment," and the "general nature and extent of risks without enumerating [them]"); N.H. REV. STAT. ANN. §§ 507-E:2(II)(b), 507C.2 (1995) ("risks or hazards inherent in such treatment"); N.J. STAT. ANN. § 26:2H-12.8(d) (West 1996) ("the specific procedure or treatment, the medically significant risks involved, and the possible duration of incapacitation," and "any medically significant alternatives"); N.C. GEN. STAT. § 90-21.13(a)(2) (1993) ("a general understanding of the procedure[]," "usual and most frequent risks"); OR. REV. STAT. § 677.097(1) (1994) ("the procedure . . . to be undertaken," "alternative procedures," and "risks"); TEX. REV. CIV. STAT. ANN. art. 4590i (Vernon 1995) (such "risks and hazards" as determined by the "Texas Medical Disclosure Panel"); VT. STAT. ANN. tit. 12 § 1909(a)(1) (Supp. 1994) ("alternatives" and "reasonably foreseeable risks and benefits"); WASH. REV. CODE ANN. § 7.70.050(3) (West 1992) ("nature and character of the treatment," "anticipated results," "recognized possible alternative[s]," "recognized serious possible risks . . . and anticipated benefits"); WIS. STAT. ANN. § 448.30 (West 1988) ("alternate, viable . . . treatment," and "benefits and risks"). *Cf.* CAL. HEALTH & SAFETY CODE § 24173 (West 1992) (applicable to medical experiments only; does not require disclosure of FDA regulatory status).

[131] N.Y. PUB. HEALTH LAW § 2805-d(1) (McKinney 1993). Section 2805-d(1) was held to be "clear and unambiguous" in Tenuto v. Lederle Laboratories, 616 N.Y.S.2d 391, 392 (App. Div. 1994), *appeal dismissed*, 662 N.E.2d 1073 (N.Y. 1995). The contrary suggestion in Retkwa v. Orentreich, 584 N.Y.S.2d 710, 712 (N.Y. Sup. Ct. 1992), that the statute has "ambiguities" permitting its extension to FDA regulatory status, is thus not well taken.

In contrast, Pennsylvania's statute requires a physician to describe the procedure and its "risks and alternatives that a reasonably prudent patient would require."[132] New York's statute takes the view that informed consent is measured by what the reasonable physician would do, but Pennsylvania's statute takes the prudent patient approach.[133] Regardless which approach a particular state follows, no statutes require a discussion of nonmedical information.[134]

The bare fact of off-label use of a device or drug carries with it no medical information, either express or implied. While patients might have some assurance that uses actually appearing on labeling are safe and effective,[135] they cannot imply from a label's silence that a particular use recommended by their physician is unsafe, risky, novel, or untried. Moreover, in the FDAMA, Congress has taken a step to ensure that information about the actual risks of off-label uses can appear on labeling for devices. Congress has provided that, under specified circumstances, FDA can

> require a statement in labeling that provides appropriate information regarding the use of the device not identified in the proposed labeling if . . . the Director determines and states in writing:
>
> (I) that there is a reasonable likelihood that the device will be used for an intended use not identified in the proposed labeling for the device, and
> (II) that such use could cause harm.[136]

Congress thus has undertaken to address the risks of off-label use directly, by providing doctors with more information about those risks. While doctors should be familiar with the risks and benefits of any course of treatment (on-label or off-label) that they propose, this amendment takes the additional step of encouraging the inclusion of information about the risks of off-label use on the label itself.

When a proposed course of medical treatment is *in fact* novel or untried, however, rendering its risks and benefits uncertain, both ethics and the law ordinarily would require that the novelty of the procedure be disclosed to the patient. "If the protocol involves innovative therapy, the physician-investigator may be held liable for failure to negotiate informed consent merely by virtue of having failed to explain that the procedure used represented a departure from customary practice."[137]

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[132] 40 PA. STAT. ANN. § 1301.811-A (Purdon Supp. 1997). Notably, the Pennsylvania statute lists "using an approved medication or device in an experimental manner," as a type of procedure for which informed consent must be obtained, but does not require that any mention be made of regulatory status. *Id.*

[133] As the Pennsylvania statute shows, even the reasonable patient approach limits material information to that concerning medical risks and benefits. *See also Canterbury*, 464 F.2d at 786-87 ("whether a particular peril must be divulged is its materiality to the patient's decision: all risks potentially affecting the decision must be unmasked").

[134] *See supra* note 130.

[135] The recent fenfluramine/dexfenfluramine recall demonstrates that an after-discovered safety issue may be determined later to outweigh the benefit of a particular labeled use. *See supra* text accompanying notes 1-5.

[136] Pub. L. No. 105-115, § 205(a), 111 Stat. at 2337 (codified at 21 U.S.C. § 360c(i)(1)(E)(i)). This section applies to 510(k) clearance, and is therefore limited to off-label uses known at the time of initial introduction. It is to be in force for a five-year trial period only. *Id.* (codified at 21 U.S.C. § 360c(i)(1)(E)(iv)). There is no comparable provision for drugs.

[137] LEVINE, *supra* note 81, at 100. *See also* Shadrick v. Coker, 1997 WL 62615, at *5 (Tenn. Feb. 17, 1998) ("patient must also be informed . . . if applicable, that the proposed treatment or procedure is experimental"); Estrada v. Jaques, 321 S.E.2d 240, 253-54 (N.C. Ct. App. 1984) (informed consent required disclosure of experimental nature of procedure when only "one article and one [previous] operation" involved the procedure); Gaston v. Hunter, 588 P.2d 326, 350-51 (Ariz. Ct. App. 1978) (while the novelty of drug therapy must be explained to patient, FDA regulatory status was properly excluded).

Novelty, however, cannot be equated with FDA regulatory status; many off-label uses of devices and drugs are widespread and generally accepted therapies.[138] Thus, in *Gaston v. Hunter*, the Arizona Court of Appeals simultaneously held that informed consent encompassed medical novelty, and affirmed exclusion of the drug's investigational FDA status as irrelevant because "[i]t would have no tendency to prove negligence on the part of the doctors or the drug companies, [and] it would not show that the plaintiff's injuries were caused by the drug."[139]

This distinction was lost in *Proctor v. Davis*,[140] a product liability case. The court characterized the off-label use in question (periocular injection of a steroid) as "experimentation;"[141] this description, however, is questionable. Although the treatment in the suit occurred in 1983, the court concentrated on events that occurred decades earlier, between 1959 and 1965.[142] While the off-label use in question was undoubtedly experimental during some, and possibly all, of this period, nothing in the opinion supports that conclusion that it remained so some twenty years later. Indeed, the facts suggest the opposite conclusion — that the off-label use had become widely-practiced and that the risk the plaintiff suffered was known and documented by the medical literature.[143] Given these facts, the experimental characterization of the off-label use in *Proctor* appears to be unjustified.[144]

Even in the context of well-known medical risks, disclosure is limited by their "materiality to the patient's decision."[145] Physicians are not required to inform patients of all known risks "however slight or immaterial."[146] A patient's interest in informed consent "does not place upon the physician a duty to elucidate upon all of the possible risks, but only those of a serious nature . . . . The law does not contemplate that a doctor need conduct a short course in anatomy, medicine, surgery, and therapeutics."[147]

These general principles underlying the doctrine of informed consent prevent physicians from having to explain nonmedical information such as FDA regulatory

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[138] *See supra* text accompanying notes 71-81 (discussing conditions for which the standard treatments are actually off-label uses).

[139] 588 P.2d at 335. In *Retkwa v. Orentreich*, 584 N.Y.S.2d at 710, a New York county court ostensibly relied on *Gaston*, but allowed what *Gaston* had expressly prohibited — evidence of FDA regulatory status in an informed consent case. *Id.* at 712-13. *Retkwa* found no other precedent for its admittedly "novel" ruling. *Id.* The medical use in *Retkwa* apparently was truly unproven, because FDA never had allowed the liquid silicone involved to be marketed for any purpose whatsoever. *Id.* at 710 n.1.

[140] 682 N.E.2d 1203 (Ill. App. Ct. 1997).

[141] *Id.* at 1213.

[142] *Id.* at 1207-09.

[143] *See id.* at 1207 n.1 (noting treating physician's testimony that "the technique of periocular injection was widely used . . . an estimated one million times each year"). The dissent discussed at length the literature addressing the relevant risks that had appeared prior to the incident at suit. *Id.* at 1219.

[144] The *Proctor* case has a remarkable procedural history, and the result was dependent on a change in the composition of the panel. *See* Proctor v. Davis, 656 N.E.2d 23 (Ill. App. Ct. 1995) (authors of majority and dissenting opinions), *invalidated by* 677 N.E.2d 918 (Ill. 1997). The tenor of the most recent *Proctor* opinions suggests to the authors that, over the course of this long appellate history, the court may have lost its ordinary sense of judicial detachment.

[145] Cobbs v. Grant, 502 P.2d 1, 11 (Cal. 1972).

[146] Hondroulis v. Schuhmacher, 553 So. 2d 398, 418-19 (La. 1988). A "detailed technical medical explanation" is not necessary. McGeshick v. Choucair, 9 F.3d 1229, 1233 (7th Cir. 1993), *cert. denied*, 116 S. Ct. 1834 (1996) (citation and quotation marks omitted). Thus, "[t]his doctrine has not emerged to educate the patient generally on medical matters." Turner v. Children's Hosp., Inc., 602 N.E.2d 423, 431 (Ohio Ct. App. 1991), *motion overruled*, 590 N.E.2d 1268 (Ohio 1992). "A mini-course in medical science is not required; the patient is concerned with the risk of death or bodily harm, and problems of recuperation." *Cobbs*, 502 P.2d at 11.

[147] Ritz v. Florida Patient's Compensation Fund, 436 So. 2d 987, 992 (Fla. Dist. Ct. App. 1983) (citation and quotation marks omitted), *appeal denied*, 450 So. 2d 488 (Fla. 1984).

status to their patients. Thus, it is to be expected that "no appellate cases have held that a physician's failure to disclose that the drug therapy was prescribed off-label violated informed consent."[148] Although all states follow this fundamental principle, it is instructive to see how a few have approached it in practice. The informed consent laws of Pennsylvania, Tennessee, Texas, Missouri, and California are illustrative.

A. *Pennsylvania*

In Pennsylvania, a physician must "advise a patient of *material* facts, risks, complications and alternatives to surgery."[149] By statute, this obligation includes "risks and alternatives that a reasonably prudent patient would require."[150] "Material" facts are limited to medical facts, such as "the nature of the therapy, the seriousness of the situation, [or] the disease and the organs involved."[151] Even as to medical facts, however, "[a] physician or surgeon need not disclose all known information."[152] Pennsylvania courts have excluded from the scope of the informed consent duty information with much more relevance to the prospects for successful treatment than FDA regulatory status.

In *Smith v. Yohe*,[153] the plaintiff complained that he had not consented to an implant in his leg. The Pennsylvania Supreme Court held the doctrine of informed consent did not require a separate discussion and a separate consent for the use of each medical device that might be employed during surgery.

> [T]he insertion of the [implant] was a part of, and a completion of, the process of relocating the parts and holding them permanently in position. Such a procedure would be analogous to placing a clamp on a wound or inserting a drain in an incision following a surgical operation, special authorization for which clearly is not required.[154]

On this basis, "the court below very properly entered a compulsory nonsuit."[155]

In *Dunham v. Wright*,[156] the court held that even an undisclosed risk of death did not demand the conclusion that surgery was performed without informed consent. As long as the patient was informed generally that both the malady and the proposed surgery were "serious," "a recital of medical casebook theory" listing every possible consequence was not required.[157]

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[148] Christopher, *supra* note 2, at 255.

[149] *See, e.g.*, Sinclair v. Block, 633 A.2d 1137, 1140 (Pa. 1993) (citation and quotation marks omitted) (emphasis in original); Gouse v. Cassel, 615 A.2d 331, 334 (Pa. 1992).

[150] 40 PA. STAT. ANN. § 1301.811-A.

[151] Festa v. Greenberg, 511 A.2d 1371, 1373 (Pa. Super. Ct. 1986), *appeal denied*, 527 A.2d 541 (Pa. 1987). *See also* Gray v. Grunnagle, 223 A.2d 663, 674 (Pa. 1966) ("informed" consent includes "the nature of the operation to be performed, the seriousness of it, the organs of the body involved, the disease or incapacity sought to be cured, [or] the possible results" of surgery) (citation and quotation marks omitted); Neal v. Lu, 530 A.2d 103, 111 (Pa. Super. Ct. 1987) (physicians must disclose "any risk in the recommended treatment, or the existence of any alternative method of treatment, that a reasonable person would deem material in deciding whether to undergo[] treatment") (citation omitted).

[152] *Gouse*, 615 A.2d at 334.

[153] 194 A.2d 167 (Pa. 1963).

[154] *Id.* at 175 (quoting trial court).

[155] *Id. See Gouse*, 615 A.2d at 334 (quoting and following *Smith v. Yohe* formulation of informed consent doctrine); Moure v. Raeuchle, 604 A.2d 1003, 1008 (Pa. 1992) (same).

[156] 423 F.2d 940, 946 (3d Cir. 1970).

[157] *Id.* at 946.

The Pennsylvania Superior Court established the boundaries of the informed consent doctrine in two court cases. In *Dible v. Vagley*,[158] the plaintiff alleged a failure of informed consent because his physician had not made him aware of a nonsurgical alternative procedure. The court disagreed, saying that "[d]espite appellant's insistence that he was injured by lack of information, the informed consent doctrine has never been applied to situations in which the missing information was other than that affecting a surgical and/or operative procedure actually performed."[159] *Dible* followed *Kaskie v. Wright*.[160] In *Kaskie*, the court affirmed summary judgment where the plaintiff alleged that his surgeon failed to disclose that he "was an alcoholic and unlicensed to practice medicine in Pennsylvania."[161] The court found no authority for enlarging the informed consent doctrine to include information beyond that directly pertaining to the risks and benefits of a particular surgery.

> Obviously, traditional analysis is somewhat removed from the facts at hand, as it is not the particular procedure performed . . . which is at issue[] here, but rather some alleged characteristics of the person performing it. The question then becomes whether the doctrine of informed consent can be expanded to include information other than that which concerns medical treatment by surgical procedure . . . .
>
> [T]here is no allegation here that appellants were uninformed about the particular procedures their son underwent irrespective of the surgeon performing them . . . . [We] refuse to expand the informed consent doctrine to include matters not specifically germane to surgical or operative treatment.[162]

The court additionally observed that, should the doctrine of informed consent be expanded beyond information material to the surgery itself, a physician's duty to provide information could well become limitless:

> To do so [expand informed consent to matters beyond risks of surgery] where the absent information consists of facts personal to the treating physician, extends the doctrine into realms well beyond its original boundaries. Nor are limitations easily definable. Are patients to be informed of every fact which might conceivably affect performance in the surgical suite?[163]

One exception to consistent Pennsylvania precedent was *Corrigan v. Methodist Hospital*,[164] a case that involved claims against a physician for failure to obtain in-

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[158] 612 A.2d 493 (Pa. Super. Ct. 1992), *appeal denied*, 629 A.2d 1380 (Pa. 1993).

[159] *Id.* at 496 (affirming summary judgment). *Dible* thus contrasts with Stover v. Association of Thoracic & Cardiovascular Surgeons, 635 A.2d 1047 (Pa. Super. Ct. 1993). In *Stover*, the court held that a surgeon discussing heart valve replacement surgery was obligated legally to inform the patient about the "risks of alternative prostheses." *Id.* at 1051. While this conclusion is arguably inconsistent with the *Smith v. Yohe*'s holding that particular medical devices need not be discussed at all, 194 A.2d at 175, *Stover* remained explicitly tied to surgical risks — specifically the risks of alternative surgical procedures.

[160] 589 A.2d 213 (Pa. Super. Ct.), *appeal denied*, 600 A.2d 954 (Pa. 1991).

[161] *Id.* at 214.

[162] *Id.* at 216-17.

[163] *Id.* at 217. *See also* Semeraro v. Connolly, C.A. No. 92-4636, 1992 WL 392621, at *2 (E.D. Pa. Dec. 14, 1992) (no claim for lack of informed consent for surgeon's alleged failure to inform patient of "[surgeon's] deteriorating sight, coordination and mental faculties"); *cf.* Grabowski v. Quigley, 684 A.2d 610, 617 (Pa. Super. Ct. 1996) ("ghost surgery" violates informed consent; nature of surgery changed by substitution of surgeon unknown to patient), *appeal granted*, 698 A.2d 594 (Pa. 1997).

[164] 869 F. Supp. 1202 (E.D. Pa. 1994).

formed consent to surgery involving off-label use of bone screws in the spinal pedicles. The court in *Corrigan* grounded its decision, to allow an informed consent claim based on FDA regulatory status, on an expert opinion that off-label use, in and of itself, "created a risk."[165] Litigation involving this product, however, later was subject to a multidistrict consolidation, and the multidistrict court expressly rejected *Corrigan*.

> [We] disagree with the court's finding in *Corrigan*. The FDA's labeling or ranking of a particular medical device for its administrative or regulatory purposes is not a "risk" of a medical procedure. Examples of "risks" of a medical procedure are internal bleeding, paralysis, or neurological damage . . . . The FDA labels given to medical devices do not speak directly to the medical issues surrounding a particular surgery. They are not, therefore, required to be disclosed pursuant to the law of informed consent.[166]

B. *Tennessee*

In Tennessee, informed consent actions are governed by the Tennessee Medical Malpractice Act.[167] Section 118 of that statute provides that

> [i]n a malpractice action, the plaintiff shall prove . . . that the defendant did not supply appropriate information to the patient in obtaining his informed consent . . . in accordance with the recognized standard of acceptable professional practice in the profession and in the specialty, if any, that the defendant practices in the community in which he practices.[168]

Under Tennessee law, a patient should be made aware of "the extent of the risks [and] the nature of the treatment" being proposed.[169] Informed consent plaintiffs have the burden of proving "(a) what a reasonable medical practitioner . . . would have disclosed to the patient about attendant risks incident to a proposed diagnosis or treatment and (b) that the defendant departed from the norm."[170]

Recitation of all possibly relevant information is not required. "A physician is not required to enumerate in detail every aspect of surgery or every possible thing that might go wrong," and a patient is not required to "take a medical course" before he or she can consent effectively to surgery.[171] Nor is informed consent required for each particular medical device or drug used in a medical procedure. "[T]he better rule is that a treating physician must obtain the patient's informed consent for the medical treatment of the patient and not for each component part of the treatment process."[172]

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[165] *Id.* at 1207.

[166] *Orthopedic Bone Screw*, 1996 WL 107556, at *3 (citation omitted).

[167] TENN. CODE ANN. § 29-26-101 et seq. (Supp. 1997).

[168] *Id.* § 29-26-118.

[169] Cardwell v. Bechtol, 724 S.W.2d 739, 750 (Tenn. 1987).

[170] *Id.* (*quoting* German v. Nichopoulos, 577 S.W.2d 197, 204 (Tenn. Ct. App. 1978), *appeal denied* (Tenn. 1979)). "[F]ailure to inform a patient of a risk that does not ripen into a condition as a result of the surgery is immaterial as to whether informed consent was given." *See* Bryant v. Bauguss, C.A. No. 03A01-9603-CV-00105, 1996 WL 465539, at *6 (Tenn. Ct. App. Aug. 16, 1996). A legal status, of course, cannot cause or be a risk, and cannot "ripen into a condition."

[171] Longmire v. Hoey, 512 S.W.2d 307, 310 (Tenn. Ct. App. 1974), *appeal denied* (Tenn. 1974).

[172] Cary v. Arrowsmith, 777 S.W.2d 8, 21 (Tenn. Ct. App. 1989) (rejecting requirement that informed consent requires separate informed consent for specific drugs used in connection with surgery).

In *Cole v. Cobb* (an unpublished decision),[173] the U.S. Court of Appeals for the Sixth Circuit found Tennessee's statutory standard of informed consent dispositive, and rejected an informed consent claim based on FDA regulatory status. "In light of this statutory language, which requires proof of professional standards . . ., we conclude that Tennessee courts would not look to the FDCA to provide a standard of professional practice concerning informed consent."[174] The *Cole* court further observed that, "even if Tennessee courts would use the FDCA in this way,"[175] FDA's informed consent regulations apply only to IDEs, not to off-label use.

> It is true that certain regulations promulgated under the FDCA address issues of informed consent in the context of clinical investigations concerning the safety and effectiveness of drugs and medical devices. [*See* 21 C.F.R. § 812.] These regulations, however, only apply to the clinical use of drugs and devices on human test subjects. They do not apply to a physician's use of drugs or devices during the course of treatment. As a result, [plaintiff] has failed to demonstrate how defendant's use of Histoacryl Blue during her treatment violated the FDCA or any regulation promulgated under it. In the absence of any proof of a statutory violation, her claim of lack of informed consent *per se* and battery *per se* must fail.[176]

Most recently, the Tennessee Supreme Court discussed experimental surgery in *Shadrick v. Coker*,[177] but only in the context of whether the discovery rule tolled the statute of limitations in an informed consent case. The facts before the court in *Shadrick* were that back surgery involving pedicle fixation with screws was "experimental" in early 1990, and that standard medical practice at that time was to inform patients of FDA regulatory status.[178] The court commented on the defendant's lack of any counteraffidavit, which required the plaintiff's uncontradicted affidavit containing those facts to be taken as true.[179] The court therefore opined that it was

> not persuaded that these facts necessarily compel a reasonable person to conclude that [plaintiff] knew or reasonably should have known that his problems were the result of wrongful or tortious conduct by [the defendant physician]. . . . [Plaintiff] was also told at the time that the screws were "routine treatment". . . . As a reasonable lay person, [plaintiff] could have believed [defendant] when he informed him that the screws were routine for use in back-fusion surgeries, especially since [defendant] had never disclosed any risks or potential complications related to the use of the screws or even their experimental nature.[180]

Although *Shadrick* referred to FDA regulatory status as one of the many disclosures the plaintiff's affiant stated were required,[181] that status was not determined. Whether

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[173] Cole v. Cobb, C.A. No. 91-5557, 1992 WL 92788, at *6 (6th Cir. May 4, 1992). *Cole* is listed in a table at 961 F.2d 1576.

[174] *Id.* at *6.

[175] *Id.*

[176] *Id.* (citation omitted).

[177] 1998 WL 62615 (Tenn. Feb. 17, 1998).

[178] *Id.* at *3.

[179] *Id.* at *3, *8.

[180] *Id.* at *7.

[181] *Id.* at n.5 (listing 23 items); *see id.* at *2-*3, *7.

the use in *Shadrick* was off-label or something else was irrelevant, because the appeal was from a statute-of-limitations-based summary judgment.[182] Because the validity of the informed consent claim was not at issue, the court did not address FDA regulatory status.[183] Whether *Shadrick* indicates a departure from *Cole* on any matter of substantive law is uncertain, and will have to await further development.

Aside from the obliquely contrary opinion in *Shadrick*, Tennessee's informed consent statute has been construed uniformly as imposing a limited duty to provide a patient with a reasonable explanation of the risks associated with a particular procedure, and never has been extended to the details of the procedure or to nonmedical information such as the legal status of medical products.

C. *Texas*

Texas informed consent law requires explanation only of risks incident to medical procedures. The scope of disclosure for medical care or surgical procedures performed after August 29, 1977, is set forth by the Medical Liability and Insurance Improvement Act (MLI).[184] Under the MLI, a Medical Disclosure Panel determines what informed consent requires for particular procedures.[185] The Panel places each procedure on one of two lists: List A (requiring disclosure) and List B (requiring no disclosure).[186] Discussion of the risks set forth on List A is a defense to an informed consent claim.[187] None of the risks contained in List A include FDA regulatory status of a device or drug. Thus, Texas law does not require a physician explain to his or her patients FDA regulatory status of a product used in any of the procedures on List A.

A physician "shall be considered to have complied with" the legal obligation to obtain informed consent[188] if he or she explains the risks "in the form and to the degree required" by List A.[189] Under the MLI, therefore, the patient's consent is "considered effective"[190] if the List A risks are discussed, regardless of any additional information that is or is not imparted by the physician. Because the Panel does not require physicians to address FDA regulatory status, the nondisclosure of that information cannot give rise to an informed consent claim under Texas law. Accordingly, an informed consent in Texas claim cannot be predicated on FDA regulatory status.

If a medical procedure is not on either list, then "the physician . . . is under the duty otherwise imposed by law."[191] The MLI defines the scope of the physician's informed consent obligation: "[T]he only theory on which recovery may be obtained is that of negligence in failing to disclose the risks or hazards that could have influenced

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[182] In other cases involving the same products, courts determined that off-label use was involved, and addressed informed consent and FDA regulatory status on the merits. *Femrite*, 568 N.W.2d at 540; *Klein*, 673 N.E.2d at 231; *Orthopedic Bone Screw*, 1996 WL 107556, at *4.

[183] The court characterized the device as "not approved" by FDA, the description contained in the plaintiff's affidavit. 1998 WL 62615, at *2-*3. That imprecise description could mean off-label use or use of products (such as injectable silicone, *see supra* note 138) without any FDA pedigree.

[184] TEX. REV. CIV. STAT. ANN. art. 4590i, § 6.02 (Vernon 1997). *See* Peterson v. Shields, 652 S.W.2d 929, 930-31 (Tex. 1983); Price v. Hurt, 711 S.W.2d 84, 88 (Tex. Ct. App. 1986).

[185] TEX. REV. CIV. STAT. ANN. art. 4590i, § 6.04(a).

[186] *See* 25 TEX. ADMIN. CODE § 601.1 (West 1995).

[187] TEX. REV. CIV. STAT. ANN. art. 4590i, § 6.05. (a physician "shall be considered to have complied" with informed consent requirements if the "disclosure is made as provided" on List A). *See* Blakesley v. Wolford, 789 F.2d 236, 239-40 (3d Cir. 1986) (describing Texas informed consent procedures).

[188] TEX. REV. CIV. STAT. ANN. art. 4590i, § 6.05.

[189] *Id.* art. 4590i, § 6.06.

[190] *Id.*

[191] *Id.* art. 4590i, § 6.07(b).

a reasonable person in making a decision to give or withhold consent."[192] To be actionable, a nondisclosure, must involve a risk that "exists in and is inseparable from the [procedure] itself."[193] If a fact is not a known risk of the procedure, the physician has no duty to bring it to the patient's attention.[194] Texas has not extended the doctrine of informed consent to information that does not affect the risks of medical treatment.[195]

D. *Missouri*

In Missouri, a physician must warn his or her patient of "risks incident to proposed treatment" in a manner sufficient to allow the patient to give informed consent to that treatment.[196] Informed consent requires that "the patient have a clear understanding of the risk and benefits of the proposed treatment, alternatives or non-treatment, along with a full understanding of the nature of the disease and the prognosis."[197] The question of which disclosures of risk should be made in a particular situation rests on "medical judgment."[198] Missouri recognizes that "[a] reasonable doctor would not necessarily disclose every possible alternative, nor would that doctor necessarily disclose all details about the risk associated with each alternative."[199]

An informed consent claim in Missouri cannot be based on a legal issue such as FDA regulatory status. The U.S. Court of Appeals for the Eighth Circuit, interpreting Missouri law in *Weaver v. Reagen*,[200] held that "FDA approved indications were not intended to limit or interfere with the practice of medicine nor to preclude physicians from using their best judgment in the interest of the patient."[201] "[D]octors commonly exercise professional medical judgment and prescribe drugs for uses not within the indications articulated by the FDA."[202] "Thus, the 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."[203]

The Eighth Circuit likewise has distinguished legal information from medical information under Missouri law, holding that legal information has no reasonable relationship to the informed consent process. The court invalidated a requirement that physicians tell abortion patients about a Missouri statute terminating their parental rights in the event of a live birth during an attempted abortion.

> [R]equiring the physician to tell his patient what will be done to accomplish the abortion and what the consequences will be assists the patient in being

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[192] *Id.* art. 4590i, § 6.02.

[193] Barclay v. Campbell, 704 S.W.2d 8, 10 (Tex. 1986).

[194] Jordan v. Geigy Pharm., 848 S.W.2d 176, 179 (Tex. Ct. App. 1992); Gibson v. Methodist Hosp., 822 S.W.2d 95, 101 (Tex. Ct. App. 1991), *writ denied* (Tex. 1992).

[195] In Texas, the statutory duty of informed consent has not even been extended to disclosure of alternative procedures. Duff v. Yelin, 721 S.W.2d 365, 372 (Tex. Ct. App. 1986), *aff'd*, 751 S.W.2d 175 (Tex. 1988).

[196] Aiken v. Clary, 396 S.W.2d 668, 674 (Mo. 1965). *Accord* Hoffman v. Rotskoff, 715 S.W.2d 538, 543 (Mo. Ct. App. 1986); Douthitt v. United States, 491 F. Supp. 891, 894 (E.D. Mo. 1980).

[197] Cruzan v. Harmon, 760 S.W.2d 408, 417 (Mo. 1988), *aff'd*, 497 U.S. 261 (1990).

[198] *Aiken*, 396 S.W.2d at 674; Eichelberger v. Barnes Hosp., 655 S.W.2d 699, 705 (Mo. Ct. App. 1983).

[199] Wilkerson v. Mid-America Cardiology, 908 S.W.2d 691, 698 (Mo. Ct. App. 1995).

[200] 886 F.2d 194 (8th Cir. 1989).

[201] *Id.* at 198.

[202] *Id.* at 199 (quotation marks omitted).

[203] *Id.* at 198.

> able to give an informed consent, [but] the requirement that the physician tell his patient of [the Missouri statute terminating their rights] is not reasonably related to the purpose of informed consent.[204]

Analogous legal information, such as a product's regulatory status, should be equally irrelevant to the informed consent process in Missouri.

D. *California*

Under California law, the obligation for physicians to obtain the informed consent of their patients does not extend to information that has no bearing on the risks and benefits of treatment. In *Cobbs v. Grant*, the California Supreme Court made clear that "as an integral part of the physician's overall obligation to the patient there is a duty of reasonable disclosure of the available choices with respect to proposed therapy and of the dangers inherently and potentially involved in each."[205] The court went on to describe the patient's "decisional process" leading to informed consent.

> A medical doctor . . . appreciates the risks inherent in the procedure he is prescribing, the risks of a decision not to undergo the treatment, and the probability of a successful outcome of the treatment . . . . The weighing of these risks against the individual subjective fears and hopes of the patient is not an expert skill . . . [, but] is a nonmedical judgment reserved to the patient alone.[206]

The court held that the recitation of all possibly relevant "material" information is not required. "[T]he patient's interest in information does not extend to a lengthy polysyllabic discourse on all possible complications. A mini-course in medical science is not required; the patient is concerned with the risk of death or bodily harm, and problems of recuperation."[207] Disclosure of "relatively minor risks inherent in common procedures" is thus necessary only in unusual circumstances. "When there is a common procedure a doctor must, of course, make such inquiries as are required to determine if for the particular patient the treatment under consideration is contraindicated . . . ; but no warning beyond such inquiries is required as to the remote possibility of death or serious bodily harm."[208] The court asserted that the test to determine "whether a potential peril must be divulged is its materiality to the patient's decision."[209] Thus, the only absolute duty of a physician is "to disclose to his patient the potential of death or serious harm, and to explain in lay terms the complications that might possibly occur."[210] Beyond this duty, whether "additional information" should be disclosed is determined by what "a skilled practitioner of good standing would provide under similar circumstances."[211]

The standards established in *Cobbs* all pertain to the risks and benefits of medical procedures. These standards have been reaffirmed by subsequent decisions of the Cali-

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[204] Freiman v. Ashcroft, 584 F.2d 247, 251 (8th Cir. 1978) (citation omitted), *aff'd*, 440 U.S. 941 (1979).
[205] 502 P.2d 1, 10 (Cal. 1972).
[206] *Id.*
[207] *Id.* at 11.
[208] *Id.*
[209] *Id.*
[210] *Id.*
[211] *Id.*

fornia Supreme Court. In *Truman v. Thomas*,[212] the court held that the obligation to obtain informed consent included informing the patient of the consequences if he or she refused to undergo a recommended diagnostic test. The court held that the information should have been disclosed because it involved the risks and benefits of medical treatment.

> If a patient indicates that he or she is going to *decline* the risk-free test or treatment, then the doctor has the additional duty of advising of all material risks of which a reasonable person would want to be informed before deciding not to undergo the procedure. On the other hand, if the recommended test or treatment is itself risky, then the physician should always explain the potential consequences of declining to follow the recommended course of action.[213]

California extended the doctrine of informed consent to its outermost limits in *Moore v. Regents of the University of California*,[214] holding that informed consent requires physicians "to disclose personal interests . . . that may affect the physician's professional judgment."[215] This conclusion was grounded in the court's concern that such considerations could affect, wittingly or unwittingly, the weighing of medical risks and benefits by the physician.

> [M]edical treatment decisions are made on the basis of proportionality — weighing the benefits to the patient against the risks to the patient . . . . A physician who adds his own research interests to this balance may be tempted to order a scientifically useful procedure or test that offers marginal, or no, benefits to the patient.[216]

Determining that a reasonable patient would want to know the factors that might be "affect[ing] the physician's judgment" of the risks and benefits of proposed medical procedures, the court held, on the facts before it, that the extensive pecuniary and research interests of the physician in that case should have been disclosed.[217]

In *Arato v. Avedon*,[218] the California Supreme Court held that the limits of doctrine of informed consent had been exceeded by a claim that a physician should have disclosed statistical life expectancy data to a patient afflicted with pancreatic cancer when the general statistics did not accurately reflect the individual patient's prognosis. The court observed that general mortality statistics "are inherently unreliable and offer little assurance regarding the fate of the individual patient."[219] "[D]eclin[ing] to intrude" on "the subtleties of the physician-patient relationship," the court refused to "requir[e] the disclosure of information that may or may not be indicated in a given treatment context."[220]

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[212] 611 P.2d 902 (Cal. 1980).

[213] *Id.* at 906 (emphasis in original).

[214] 793 P.2d 479 (Cal. 1990).

[215] *Id.* at 483.

[216] *Id.* at 484.

[217] *Id.* Without the patient's knowledge, the physician in *Moore* utilized the patient's tissue in private research that allegedly had a potential market value of several billion dollars. *Id.* at 482.

[218] 858 P.2d 598 (Cal. 1993).

[219] *Id.* at 607.

[220] *Id.*

The *Arato* court rejected expansion of the doctrine of informed consent to general information not relevant to the medical interest of an individual patient. The court explained that the "patient's right of self decision" protected by the doctrine of informed consent "presuppos[es] a therapeutic focus."[221] The broader definition of materiality that the plaintiffs advocated "failed to reflect the therapeutic limitation inherent in the doctrine of informed consent;"
"[t]he fact that a physician has 'fiducial' obligations . . . does not mean that he or she is under a duty, the scope of which is undefined, to disclose every contingency that might affect the patient's *nonmedical* 'rights and interests.'"[222] Most recently, in *Daum v. Spinecare Medical Group*,[223] an IDE device case, the California Court of Appeals noted that the failure to inform the plaintiff of the investigational status of an IDE device would not have been actionable, if only the common law had been involved in the case.

> Our Supreme Court has refrained from prescribing specific disclosures by physicians to patients . . . . However, the legislature and the FDA, in their wisdom, have decreed that patients participating in clinical trials of investigational devices must be informed in writing, with a copy for themselves, of the nature and the device. Neither physicians nor courts are free to disregard these requirements . . . .
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> [Defendant] argues that . . . the statutory requirements do not differ in any significant extent from the common-law informed consent standards . . . . We disagree . . . . [T]he statute makes significant procedural additions to the general common-law requirements.[224]

The court's point of disagreement in *Daum* is precisely what distinguishes federal informed consent requirements for patients enrolled in clinical trials from state informed consent requirements for what is simply off-label use.[225]

In the two decades since *Cobbs* was decided, the evolving doctrine of informed consent in California never has been construed to encompass information that does not in some way affect the risks and benefits of medical treatments (actual or proposed).[226] Even *Moore*, which probed the limits of informed consent in California, involved disclosure of information that involved risk to a patient.

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[221] *Id.* at 608.

[222] *Id.* at 609 (citation and footnote omitted) (emphasis in original). A physician "is not the patient's financial advisor." *Id.* (citation and quotation marks omitted). Nor is a physician required to give legal advice. *See Moore*, 793 P.2d at 522 (physicians not "competent to explain esoteric questions of law") (Mosk, J. dissenting).

[223] 61 Cal. Rptr. 2d 260 (Cal. Ct. App. 1997).

[224] *Id.* at 271, 273.

[225] *See supra* notes 40, 45, 112.

[226] Other opinions of the California Court of Appeals likewise have limited informed consent liability. *See* Spann v. Irwin Mem'l Blood Ctrs., 40 Cal. Rptr. 2d 360, 368 (Cal. Ct. App. 1995) (no duty to disclose the theoretical possibility of a blood donor reduction program that the physician "had no professional duty to maintain"); Munro v. Regents of the Univ. of Ca., 263 Cal. Rptr. 878, 885 (Cal. Ct. App. 1989) (no liability for failing to disclose the heightened incidence of Tay-Sachs disease in certain population groups, when the physician had no information suggesting that the plaintiffs belonged to any of those groups); Scalere v. Stenson, 260 Cal. Rptr. 152, 159-60 (Cal. Ct. App. 1989) (no duty to disclose risks and benefits of further treatment when the physician did not recommend any further treatment); McKinney v. Nash, 174 Cal. Rptr. 642, 648 (Cal. Ct. App. 1981) (informed consent required warnings against current risks of medical treatment, but not against a surgical risk that had been eliminated or against extremely rare idiosyncratic reactions).

VI. SOUND PUBLIC POLICY WEIGHS AGAINST EXPANDING INFORMED CONSENT LAWS TO INCLUDE MEDICALLY IRRELEVANT INFORMATION

Examination of state informed consent laws thus reveals that a physician's duty is almost universally limited to providing medical information. There is no duty obligating a physician to discuss FDA regulatory status of products being used for a particular treatment,[227] because FDA regulatory status is not a risk, benefit, or alternative of medical treatment, nor does a product's legal status affect the nature of the treatment. In addition to state and federal law, logic and sound policy concerns further weigh against any expansion of the doctrine of informed consent into the legal arena of FDA regulatory status, particularly when that expansion is based on, and would exacerbate, misperceptions about the significance of that status.

To broaden informed consent to include FDA regulatory status of medical devices and drugs would require physicians first to learn and then to explain a complex set of regulations having little, if any, relationship to the risks of individualized medical treatment. Simply keeping abreast of medical advances is already a full-time job. Physicians also should not have to become experts in how FDA regulates medical devices and drugs — which they would have to do to relate any given off-label use to medical risks or benefits.[228] When a physician decides to treat a patient with a device or drug, his or her proper concern is whether the product will benefit the specific patient. Whether or not it requires a prescription; was grandfathered or generic; is Class I, II, or III; or is being used on-label or off-label is not germane to the practice of medicine. If the physician's considered professional judgment is that a particular use of a particular product is the best treatment for a particular patient, professional responsibility demands that this course of treatment be followed.

FDA status information is not readily accessible from labeling. An affirmative FDA finding that a use is *not* safe or is *not* effective would be relevant to evaluating the risks of a proposed course of treatment, but such an agency decision cannot be inferred from the mere omission of an indication from FDA-regulated labeling, and ordinarily would be recorded directly as a labeled contraindication.[229] "Thus, the 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."[230] An in-depth review of FDA regulatory history, and not a quick review of the drug or device labeling, would be required to understand why a particular use is off-label.

Physicians read medical journals, not the *Code of Federal Regulations*. Their training is in the treatment of diseases, not in the interpretation of administrative regulations or FDA guidance documents. They attend continuing medical education courses; they do not scan the *Federal Register* for notices of the latest FDA regulatory change. In short, not only are physicians already deluged with medically relevant information, they are ill-equipped to become familiar with the complex and constantly changing FDA regulatory status of the hundreds of devices and drugs that they use in their practices.

Physicians already must inform their patients about the nature of any proposed medical treatment, and of material risks and benefits. Precisely because FDA regula-

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[227] A single course of treatment frequently involves many FDA-regulated drugs or devices.

[228] *See supra* text accompanying notes 93-107.

[229] *See id.*

[230] *Weaver*, 886 F.2d at 198.

tory status is not medical information, it is not the type of information that physicians ordinarily discuss with their patients. "[I]t is not general medical practice to inform a patient whether or not a drug is FDA approved."[231] If informed consent were expanded to include a product's legal status, the number of potential informed consent claims that such a new duty would generate would be large, given the ubiquity of off-label use. Nothing would be gained, and much valuable time would be lost, if physicians had to divert their energies from treating their patients and keeping abreast of medical advances to reviewing FDA administrative law.

Just as there is a limit to the amount of information physicians can be expected to digest and explain, there is likewise a limit to what patients can absorb, particularly in what are often trying and emotional circumstances. The last thing a patient needs is irrelevant and potentially misleading information. The patient's interest in medical information is not served by a minicourse in medicine.[232] Even less do patients need a course in the federal regulation of medical devices and drugs — particularly one that inaccurately suggests that accepted off-label therapies are investigational or experimental.

Because which medical device or drug might injure which patient is not predictable, physicians would feel a legal obligation to describe FDA regulatory status of all (or virtually all) items that they propose to use. This flood of regulatory information actually could reduce the force of relevant information relating to medical issues. For precisely this reason, FDA long has refused to clutter the instructions accompanying drugs and medical devices with unnecessary information. The agency has asserted that "[t]he Commissioner does not believe that a warning or cautionary statement should be required for every possible question that might be raised about the safety of a product. A plethora of warnings about insubstantial questions would be difficult for consumers to evaluate."[233] Most patients understandably would believe that, if their physicians took the time to explain FDA regulatory status, such information must be important to their health. Patients thus would be distracted from learning about the nature, risks, and benefits of their treatments by regulatory information of *de minimus* value. Such information would accentuate the errant notion that all off-label use is by definition inherently risky, novel, or investigational. By implying risk or novelty when there is none, these disclosures could frighten patients away from the very therapies that actually are best for the treatment of their conditions.[234]

To provide an accurate picture to their patients, physicians would be placed in an awkward and confusing position. Having just laboriously described FDA regulatory status of devices or drugs proposed to be used off-label, a physician then would have to explain that this information actually is irrelevant to the patient's individual medical condition and that off-label use is, in fact, optimal. Making FDA regulatory status a mandatory part of informed consent discussions would only confuse patients and unnecessarily complicate their decisionmaking process.

Physicians still are free to go beyond the minimum required to avoid civil liability. If physicians decide to discuss the legal status of a product with a particular patient, that is their prerogative. As a matter of sound policy, however, courts should not

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[231] *Simeon Management Corp.*, 391 F. Supp. at 705.

[232] *Longmire*, 512 S.W.2d at 310; *see infra* text accompanying note 234.

[233] 43 Fed. Reg. 1101, 1104 (Jan. 6, 1978).

[234] "There is no rational reason . . . that justifies forcing physicians to give [patients] information that the physician considers injurious to the [patient's] health or simply untrue." Planned Parenthood Ass'n v. Ashcroft, 655 F.2d 848, 868 (8th Cir. 1981) (citation omitted), *aff'd in part and rev'd in part on other grounds*, 462 U.S. 476 (1983).

force physicians to take this approach with every patient, regardless of individual circumstance.

VII. THE SHAPE OF THINGS TO COME

If the philosophical underpinning of the informed consent doctrine is to ensure that patients receive necessary information about treatment, risks, and benefits, the question becomes how can a physician obtain the necessary information about a product he or she desires to use off-label? In its effort to maintain a policy against promotion of off-label uses by product manufacturers, FDA has interpreted "promotion" (undefined in the FDCA) expansively to include "a broad array of information disseminated by companies,"[235] thus substantially interfering with manufacturers' ability to provide information about off-label uses to willing physicians.

FDA attempts to curtail the availability of information about off-label uses has impacted even the Internet, with the agency considering restrictions on manufacturer web sites.[236] Such restrictions, regardless of their constitutionality,[237] are inconsistent with the evolving health-care landscape, which is increasing both the responsibility and the resources of patients with respect to the selection and evaluation of their care.[238] Many patients naturally assume responsibility for their care, and wish to use the Internet to obtain information about diseases, treatments, and health care providers.[239] The key is to provide relevant, focused information. As a presidential advisory commission recently stated, "[r]esearch on how consumers use information to make decisions suggests that too much information can be overwhelming . . . . [L]imiting information to only a few indicators of quality will probably be necessary because people can consider only a few items at any one time."[240]

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[235] 59 Fed. Reg. at 59,822. "Manufacturers cannot proactively discuss off-label uses, nor may they distribute written materials (promotional pieces, reprints of articles, etc.) that mention off-label uses." Woodcock, *supra* note 105, at 4 <http://www.fda.gov/cder/present/diamontreal/regappr/sld004.htm>; Rayburn, *supra* note 83, at 1053 ("[I]n the absence of formal approval, education and targeted marketing efforts [are] either hampered or discouraged").

[236] *See* 62 Fed. Reg. 14,912, 14,917 (Mar. 28, 1997); 61 Fed. Reg. 48,707, 48,708-09 (Sept. 16, 1996); Marc J. Scheineson, *Legal Overview of Likely FDA Regulation of Internet Promotion*, 51 FOOD & DRUG L.J. 697, 709 (1996) (parsing manufacturer web pages between labeling and promotion).

[237] FDA's obstruction of medically-related communication has led some to question the validity of the agency's position on promotion of off-label uses under the First Amendment. *See, e.g., Washington Legal Found.*, 880 F. Supp. at 34-36; BAD PRESCRIPTION, *supra* note 66, at 43-58; Edmund Polubinski III, Note, *Closing the Channels of Communication: A First Amendment Analysis of the FDA's Policy on Manufacturer Promotion of "Off-Label" Use*, 83 VA. L. REV. 991, 1010-34 (1997); Richard M. Cooper, *Unapproved Uses of Drugs: An Analysis and Some Proposals*, 49 FOOD & DRUG L.J. 533, 537 (1994). For an FDA response, see 62 Fed. Reg. 64,074, 64,076-82 (Dec. 3, 1997).

[238] *See, e.g.*, ADVISORY COMM. ON CONSUMER PROTECTION AND QUALITY IN THE HEALTH CARE INDUS., REPORT TO THE PRESIDENT: CONSUMER BILL OF RIGHTS AND RESPONSIBILITIES (1997) [hereinafter CONSUMER BILL OF RIGHTS] (especially chapters 1, 4, and 8, discussing the need for informed patient decisionmaking, the need for risk/benefit information concerning medical options, and patients' responsibility to be aware of limits of medicine and to comply with treatment programs); Greg Borzo, *"PCASSO" with a Mouse*, 24 AM. MED. NEWS, Oct. 13, 1997, at 24 (discussing the Internet's effect on health care delivery systems and its utility in "bring[ing] patients into the loop . . . to tak[e] responsibility for themselves").

[239] Medical information abounds on the Internet, demonstrating the futility of FDA's attempt to restrict discussion of off-label use by manufacturers. *See, e.g.*, Mark Perkiss, *Patients Seek Their Cure on the Net*, TRENTON TIMES, Dec. 22, 1997, at C1; Amy Lavalley, *Medical Group Sets up Shingle on Web*, NEWS LEADER, July 17, 1996, at A6; David Hayes, *Medical Facts Plentiful on Internet*, KAN. CITY STAR, June 9, 1996, at F9; Aggi Raeder, *Finding Medical Information (on the Internet)*, 4 SEARCHER 40 (1996) (listing Internet medical sources).

[240] CONSUMER BILL OF RIGHTS, *supra* note 238, at 23 (citations and quotation marks omitted).

Medical and other groups have complained that physicians cannot get the information they need because of FDA's overly restrictive rules.[241] At the 1997 annual meeting of the American Medical Association (AMA), delegates directed the AMA to seek to persuade FDA to "ensure physicians have greater access to information about unlabeled (off-label) uses of medications," citing the "prevalence and clinical importance of prescribing drugs for unlabeled uses . . . and the critical need for physicians to have access to accurate and unbiased information about unlabeled uses of prescription drugs."[242] The AMA supported the "dissemination by manufacturers of independently derived scientific information about unlabeled uses."[243]

The FDAMA responds to some of these concerns. Signed into law on November 21, 1997, the FDAMA permits manufacturers to provide physicians with certain types of information regarding off-label uses. Section 401 of the FDAMA allows manufacturers to send information about off-label uses to health care providers,[244] provided that information comes from a scientific source.[245] FDA is to review and monitor the information to ensure balanced and objective presentation.[246] In return, manufacturers

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[241] *See, e.g., DHHS Accepts Private Sector Patient Education Plan; USP Commits Support*, STANDARD, Jan. 1997, *available at* <http://www.usp.org/pubs/standard/97jan/cover.htm> (U.S. Pharmacopeial Convention supports access to off-label use information); John Merline, *Firms Contend with Worst 10 Washington Regulations*, INVESTOR'S BUSINESS DAILY, Aug. 20, 1996, at A4, *available at* <http://www.schoolreport.com/AdTI/policies/ deregulation/10woribd.htm> ("By forbidding manufacturers from spreading the word [about off-label uses], needless illnesses and deaths are occurring"); Sam Kazman, *Cardiac and Cancer Specialists on the Need for FDA Reform*, *in* COMPETITIVE ENTER. INST., DEATH BY REGULATION (1996), *available at* <http://www/cei.org/essays/kazman1.html> (polls of surgeons and oncologists demonstrate "overwhelming opposition to FDA's policy of restricting information about off-label use, and strong support for making unapproved therapies available to physicians").

[242] *AMA Supports Greater Physician Access to Unlabeled Use Information*, STANDARD, July 1997, *available at* <http://www.usp.org/pubs/standard/97jul/ama.htm>.

[243] *Id.*

[244] Under section 551(a) of the FDCA, the following audiences may receive information from manufacturers about off-label uses: "(1) a health care practitioner; (2) a pharmacy benefit manager; (3) a health insurance issuer; (4) a group health plan; or (5) a Federal or State governmental agency." Pub. L. No. 105-115, § 401, 111 Stat. at 2356-57 (codified at 21 U.S.C. § 360aaa).

[245] Section 552 of the FDCA allows manufacturers to disseminate written information about off-label uses, provided that information is "unabridged" and is in the form of published, peer-reviewed articles or generally available "reference publication[s]." *Id.* at 2358 (codified at 21 U.S.C. § 360aaa-1). The manufacturer also must

> include[] along with the information . . . . (A) a prominently displayed statement that discloses — (i) that the information concerns a use of a drug or device that has not been approved or cleared by the [FDA]; (ii) if applicable, that the information is being disseminated at the expense of the manufacturer; (iii) if applicable, the name of any authors of the information who are employees of, or consultants to, or have received compensation from, the manufacturer or who have a significant financial interest in the manufacturer; (iv) the official labeling for the drug or device and all updates with respect to the labeling; if applicable, a statement that there are products or treatments that have been approved or cleared for the use that is the subject of the information . . . ; and (vi) the identification of any person who has provided funding for the conduct of a study relating to the new use of [the] drug or device . . . ; and (B) a bibliography of other articles from a scientific reference publication or scientific or medical journal that have been previously published about the use of the drug or device covered by the information disseminated.
>
> *Id.* at 2357 (codified at 21 U.S.C. § 360aaa(b)(6) (FDCA § 551(b)(6))).

[246] Section 551(c) of the FDCA provides for FDA review. If FDA concludes that the information "fails to provide data, analyses, or other written material that is objective and balanced," it may require the manufacturer to include

> 1) additional objective and scientifically sound information that pertains to the safety or effectiveness of the use and is necessary to provide objectivity and balance . . .; and 2) an objective statement of the Secretary, based on data or other scientifically sound information . . ., that bears on the safety or effectiveness of the new use of the drug or device.
>
> *Id.* at 2358 (codified at 21 U.S.C. § 360aaa(c)).

must agree to submit a supplemental application to include those off-label uses so publicized on their labels.[247] Exceptions are provided for situations in which it is "economically prohibitive" to file a supplemental application, or in which the off-label use is so well accepted that "it would be unethical to conduct the studies" and thereby deprive the control patients of accepted forms of therapy.[248]

As are most political compromises, the FDAMA is rather cumbersome, but it does provide an avenue by which drug and device manufacturers can provide information about off-label uses of their products to the medical community without fear of adverse FDA regulatory consequences. When off-label uses are likely to be significant, manufacturers will have the economic incentive to utilize these provisions. The FDAMA thus addresses informational concerns about the risks, benefits, and alternatives to off-label uses directly, by providing for dissemination of substantive information. In light of this statute, there is even less justification for expanding the common-law doctrine of informed consent to include FDA regulatory status, because information directly pertinent to the medical concerns that underlie the informed consent doctrine should be even more readily available to physicians in the future than it has been in the past.

VIII. CONCLUSION

Most physicians carefully consider any treatment involving off-label drugs or medical devices. Both medical ethics and the doctrine of informed consent already require this. Physicians undertake a risk/benefit analysis of proposed treatments, whether they are on-label or off-label, based on their assessment of the unique medical needs of individual patients. FDA labeling has very little to do with this decisionmaking process.[249] When a patient performs his or her own risk-benefit analysis as part of the informed consent process, he or she needs certain essential information to decide whether to accept a proposed course of treatment. The patient needs to know what the treatment is, how the treatment can help, whether and how it can hurt, and what alternatives are available. The FDAMA is a step in the right direction, and its beneficial purpose should not be undercut by imposing unnecessary and counterproductive common law obstacles to off-label use. At this sensitive juncture, a patient does not need extraneous, irrelevant, or potentially misleading information. Neither medicine nor the law can afford to adopt policies based on myths and misperceptions about off-label treatment.

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[247] Section 554 (a), (c) of the FDCA requires manufacturers who wish to disseminate information about off-label uses either to have a supplemental application on file with FDA, or to file such an application within a fixed period of time if the necessary studies are incomplete. *Id.* at 2359-60 (codified at 21 U.S.C. § 360aaa-3(a)-(c)).

[248] *Id.* at 2360-61 (codified at 21 U.S.C. § 360aaa-3(d) (FDCA § 554(d))).

[249] A recent survey of physicians indicates that "85% of the doctors said FDA labels have 'little influence' or 'practically no influence at all' in their treatment of patients." Marlene Cimons, *FDA's Approval Process Faces Challenge in New Senate Bill*, L.A. TIMES, July 22, 1997, at A5.