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# THE CASE FOR LEGAL REGULATION OF PHYSICIANS' OFF-LABEL PRESCRIBING

*Philip M. Rosoff\* & Doriane Lambelet Coleman†*

## INTRODUCTION

Prescription drugs and biologics<sup>1</sup> can be used on- and off-label. On-label signifies that the particular use to which the drug is being put has been vetted by the Food and Drug Administration (FDA) through a series of trials or studies designed to establish the use's safety and efficacy.<sup>2</sup> Off-label use signifies that the particular use to which the drug is being put has not been formally approved by the FDA<sup>3</sup> and thus, unless it has been otherwise tested, its safety and effi-

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1 Drugs, or pharmaceuticals, generally include both small molecules generated by chemical manufacturing processes as well as "natural" products such as some antibiotics isolated from bacterial or fungal cultures. Biologics refer to therapies that are purified natural products (generally of mammalian origin) such as some blood components as well as those therapeutics produced by genetic engineering and biotechnology that mimic or are identical to naturally occurring proteins. See Edward L. Korwek, *What Are Biologics? A Comparative Legislative, Regulatory and Scientific Analysis*, 62 FOOD & DRUG L.J. 257, 259–60 (2007) (providing background for statutory definitions of biologics).

2 See *Off-Label Drug Use*, AM. CANCER SOC'Y, [http://www.cancer.org/docroot/ETO/content/ETO\\_1\\_2x\\_Off-Label\\_Drug\\_Use.asp](http://www.cancer.org/docroot/ETO/content/ETO_1_2x_Off-Label_Drug_Use.asp) (last visited Feb. 11, 2011). The FDA does not establish a drug's safety and efficacy for general purposes, but only for the particular use or uses identified by its manufacturer for formal marketing purposes. See *id.*

3 See *id.*

cacy for that use has not been established.<sup>4</sup> Typical off-label uses (OLU) include promoting, prescribing, and ingesting substances for conditions other than those for which they were approved, in higher- or lower-than-indicated dosages, and in populations other than those in which they were tested.<sup>5</sup>

Pharmaceutical companies are largely prohibited from promoting their products' OLU.<sup>6</sup> However, OLU are otherwise legal. That is, notwithstanding a lack of evidence of safety and efficacy, physicians may lawfully prescribe and patients may lawfully take OLU.<sup>7</sup> As a

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4 See *infra* note 15 and accompanying text (discussing other testing possibilities).

5 See *Off-Label Drug Use*, *supra* note 2; see also William L. Christopher, *Off-Label Drug Prescription: Filling the Regulatory Vacuum*, 48 FOOD & DRUG L.J. 247, 248 (1993) (suggesting that off-label uses might include using approved drugs for nonapproved diseases or varying from the indicated dosage, regimen, or patient population); Rebecca Dresser & Joel Frader, *Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, 37 J.L. MED. & ETHICS 476, 476–78 (2009) (describing physicians' discretion in prescribing drugs at dosages or using methods of administration not specified on the label).

6 See Kaspar J. Stoffelmayr, Comment, *Products Liability and "Off-Label" Uses of Prescription Drugs*, 63 U. CHI. L. REV. 275, 279 (1996). Recent regulations have been proposed which may erode this strict policy. See *Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices*, FDA (Jan. 2009), <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm> ("FDA recognizes that the public health can be served when health care professionals receive truthful and non-misleading scientific and medical information on unapproved uses of approved or cleared medical products. Accordingly, if a manufacturer follows the recommendations described in . . . this guidance, FDA does not intend to consider the distribution of such medical and scientific information . . . as establishing [prohibited] intent that the product be used for an unapproved new use."). Criticism of this "new" proposal and its potential for abuse by drug manufacturers predates this regulation by forty-seven years. See Charles D. May, *Selling Drugs by "Educating" Physicians*, 36 J. MED. EDUC. 1, 22 (1961) (discouraging drug manufacturers' "artful attempts to enlist physicians in the sale of drugs by disguising promotion as 'education'"); see also Jim Edwards, *FDA to Allow "Off-Label" Unapproved Drug Promotion*, BNET (Jan. 13, 2009), <http://industry.bnet.com/pharma/1000591/fda-to-allow-off-label-unapproved-drug-promotion> (noting that this new approach is not about protecting patients from unsupported OLU but "about trying to reduce the amount of responsibility companies have for their own drugs," and that the result is that "you can expect a new flood of drug company sponsored, peer-reviewed literature to hit the market on off-label uses"); *infra* note 37 and accompanying text (discussing companies' financial sponsorship of ghost-written articles destined for peer-reviewed publications).

7 See *Off-Label Drug Use*, *supra* note 2. Once a drug is approved by the FDA, physicians are free to use it however they wish for the benefit of their (individual) patients. This includes the situations for which the drug was tested and approved, as well as others that the doctor, in her clinical judgment, believes would be appropriate. See Christopher, *supra* note 5, at 248; David A. Kessler, *Regulating the Prescribing of Human Drugs for Nonapproved Uses Under the Food, Drug, and Cosmetic Act*, 15 HARV. J. ON

result, it is estimated that OLU account for up to twenty-one percent of drugs and biologics used annually in the United States; this figure is significantly higher in certain specialized settings such as oncology and pediatrics.<sup>8</sup>

It is likely the case that most people are unaware of the distinction between on- and off-label uses.<sup>9</sup> It is also likely that when physicians prescribe drugs for an off-label use, their patients are unaware of this fact or (correspondingly) that they may not be safe or effective.<sup>10</sup> Patients' lack of awareness is due at least in part to standard medical practice, which is not to disclose the OLU status of drugs to patients.<sup>11</sup>

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LEGIS. 693, 698 (1978); Paul W. Radensky et al., *Potential Liability for Drug Companies, Health Care Providers, and Insurers: Off-Label Prescribing and Internet Advertising*, in PHARMACEUTICAL LAW 239, 254 (Michael E. Clark ed., 2007).

8 See David C. Radley et al., *Off-Label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1025 (2006) (providing the figure of twenty-one percent); Steven R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, 51 FLA. L. REV. 181, 193 (1999) (reporting on "[o]ne estimate suggest[ing] that between twenty and sixty percent of all prescriptions are for off-label uses"). Some studies have estimated that the majority of prescriptions for anticancer drugs and drugs for children are for uses not approved by the FDA. See Am. Acad. of Pediatrics, *Uses of Drugs Not Described in the Package Insert (Off-Label Uses)*, 110 PEDIATRICS 181, 181 (2002); Radley et al., *supra*, at 1022–26; Michael Soares, *"Off-Label" Indications for Oncology Drug Use and Compendia: History and Current Status*, 1 J. ONCOLOGY PRAC. 102, 104 (2005). Surrey M. Walton reviewed national OLU and concluded that a significant percentage of such prescribing lacked any significant evidentiary support. See Surrey M. Walton et al., *Prioritizing Future Research on Off-Label Prescribing: Results of a Quantitative Evaluation*, 28 PHARMACOTHERAPY 1443, 1443–51 (2008).

9 See *Many People Think That Drugs Should Only Be Prescribed per FDA-Approved Use, Not for Off-Label Use*, HARRIS INTERACTIVE (June 9, 2004), <http://www.harrisi.org/news/allnewsbydate.asp?newsId=808> [hereinafter WSJ/Harris Poll] (reporting on the results of a poll conducted for the Wall Street Journal and concluding that "[o]ff-label prescribing' . . . is probably not an issue which many people have thought about"); see also Margaret Z. Johns, *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, 58 HASTINGS L.J. 967, 968 (2007) (discussing this poll); *infra* note 87 and accompanying text (discussing this point); see also May, *supra* note 6; Michelle M. Mello et al., *Shifting Terrain in the Regulation of Off-Label Promotion of Pharmaceuticals*, 360 NEW ENG. J. MED. 1557 (2009).

10 See Johns, *supra* note 9, at 968 ("A majority of patients believe that doctors always prescribe drugs as approved by the FDA."); *id.* at 1013 ("[T]he patient thinks the drug has been proven safe and effective for the prescribed treatment following rigorous scrutiny by the FDA, but with off-label uses it has not."); WSJ/Harris Poll, *supra* note 9 ("A 51% to 31% majority believes, wrongly, that a doctor can prescribe drugs only for the diseases for which they have been approved . . . and that . . . [a] 48% to 31% plurality believes that doctors 'should not be allowed' to prescribe a drug for diseases for which that drug has not been approved by the FDA . . .").

11 See James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 FOOD & DRUG L.J. 71, 71–72, 76, 86–91

Depending on the physician, this practice has at least two explanations: some physicians believe it is unnecessary for patients to know of their drugs' OLU status,<sup>12</sup> while others are—like their patients—ignorant of that status and thus of the safety and efficacy of the drugs they prescribe.<sup>13</sup>

Previous commentators have established up to four categories of OLU depending upon the evidentiary basis supporting their safety and efficacy: OLU justified by high-quality evidence, OLU justified by some but not high-quality evidence, OLU justified by the need or desire to innovate, and unjustified OLU.<sup>14</sup> OLU are justified by high-quality evidence of safety and efficacy using clinical investigation techniques not dissimilar to those employed by pharmaceutical companies applying for FDA approval.<sup>15</sup>

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(1998); W.A. Meadows & B.D. Hollowell, *'Off-label' Drug Use: An FDA Regulatory Term, Not a Negative Implication of Its Medical Use*, 20 INT'L J. IMPOTENCE RES. 135, 140 (2008).

12 See, e.g., Beck & Azari, *supra* note 11, at 87–89; Meadows & Hollowell, *supra* note 11, at 139–40.

13 See Donna T. Chen et al., *U.S. Physician Knowledge of the FDA-Approved Indications and Evidence Base for Commonly Prescribed Drugs: Results of a National Survey*, 18 PHARMACOEPIDEMOLOGY & DRUG SAFETY 1094, 1094–99 (2009). As one commentator notes, “[d]octors generally don’t tell people that they’re prescribing drugs pitched to them by pharmaceutical salespeople for unapproved treatments . . . . [In fact,] [m]ost physicians don’t keep track of FDA-approved uses of drugs . . . . ‘The great majority of doctors have no idea; they don’t even understand the distinction between on- and off-labeling.’” David Evans, *Pfizer Broke the Law by Promoting Drugs for Unapproved Uses*, BLOOMBERG (Nov. 9, 2009), <http://www.bloomberg.com/apps/news?pid=newsarchive&sid=A4yV1nYxCGoA> (quoting Peter Lurie).

14 Although not always using this particular phraseology, several previous commentators have established the equivalent of these categories, which track the push toward evidence-based medicine more generally. See, e.g., Amy P. Abernethy et al., *Systematic Review: Reliability of Compendia Methods for Off-Label Oncology Indications*, 150 ANNALS INTERNAL MED. 336, 336–43 (2009); Nicole Ansani et al., *Designing a Strategy to Promote Safe, Innovative Off-Label Use of Medications*, 21 AM. J. MED. QUALITY 255, 255–61 (2006); Nicole Ansani et al., *United States Medical Practice Summary: Innovative Off-Label Medication Use*, 21 AM. J. MED. QUALITY 246, 246–54 (2006); Madlen Gazarian et al., *Off-Label Use of Medicines: Consensus Recommendations for Evaluating Appropriateness*, 185 MED. J. AUSTR. 544, 546 (2006); see also Lars Noah, *Medicine’s Epistemology: Mapping the Haphazard Diffusion of Knowledge in the Biomedical Community*, 44 ARIZ. L. REV. 373, 381 (2002) (noting that “[b]y constructing a rough hierarchy that reflects the value of the different types of clinically-relevant information, evidence-based medicine attempts to improve decisionmaking by practicing physicians” and explaining that “[w]hen faced with a clinical problem, health care professionals should, in descending order of preference, look for guidance in systematic reviews of randomized controlled trials, the results of individual controlled clinical trials, observational (uncontrolled) studies, and anecdotal reports of clinical observations”).

15 For instance, this could include the design and performance of high-quality, statistically valid clinical trials. There are also methods of slower, incremental accrual

OLU whose safety and efficacy have not been established by such clinical investigation techniques (problematic OLU) can cause significant harms: They can cause physical harm (including death) to patients both directly, if they turn out to be unsafe,<sup>16</sup> and indirectly, when they are ineffective and used in lieu of an existing, established alternative.<sup>17</sup> Patients also suffer harm when their physicians prescribe problematic OLU without disclosing in advance the relevant facts about the drug's off-label status and the dearth of evidence concerning safety and efficacy. Two related patient rights are violated in this setting.

First, patients have the right to decide for themselves (as part of the informed consent process) whether or not they will accept particular medical treatment; long gone are the days when the law and medical ethics permitted physicians to make treatment decisions for their patients without ensuring in advance that they knowingly and voluntarily understood and accepted the associated risks and benefits.<sup>18</sup> Modern physicians have a corresponding legal and ethical duty to disclose all of the facts that are material to their patients' treatment decisions.<sup>19</sup> Although the argument to the contrary has been strangely

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of validated evidence for and against an OLU, often compiled by such databases as the Cochrane Collaborative. See M.C. Brouwers et al., *Evidence-Based Health Care and the Cochrane Collaboration*, 5 CLINICAL PERFORMANCE QUALITY HEALTH CARE, 195, 195–201 (1997).

16 See A.M. Gordon & B.K. Logan, *Topiramate-Positive Death-Investigation and Impaired-Driving Cases in Washington State*, 30 J. ANALYTICAL TOXICOLOGY 599 (2006) (discussing a study showing that topiramate (Topamax), a drug that was FDA-approved for use in seizure disorders (epilepsy), and which was very popular for OLU, was involved in a seemingly disproportionate number and percentage of cases referred to a state lab in Washington State, suggesting that excessive OLU was causally responsible); Lisa A. Ladewski et al., *Dissemination of Information on Potentially Fatal Adverse Drug Reactions for Cancer Drugs from 2000 to 2002*, 21 J. CLINICAL ONCOLOGY 3859, 3859–64 (2003) (discussing a study showing that serious, including fatal, adverse drug reactions that were not known upon FDA approval for the original indication, can show up even years later; and calling for expanded and increased vigilance to accrue data on the potential danger of these drugs used both on- and off-label); Gina Kolata, *Drug that Stops Bleeding Shows Off-Label Dangers*, N.Y. TIMES, Apr. 19, 2011, at D1.

17 See *infra* note 71 (discussing the case of Rituximab or Rituxan in this regard).

18 See Kolata, *supra* note 16; *infra* notes 113–20 and accompanying text (discussing this doctrine and its history).

19 See *Goldberg v. Boone*, 912 A.2d 698, 716 (Md. 2006) (“[A] claim for lack of informed consent focuses . . . on the adequacy of the explanation given by the physician in obtaining the patient’s consent.’ Therefore, the level of disclosure that is required to be given by the physician is ‘measured by the patient’s need, and that need is whatever is material to the decision.’” (second alteration in original) (citation omitted) (quoting *Dingle v. Belin*, 749 A.2d 157, 165 (Md. 2002))); see also *id.* (citing

successful,<sup>20</sup> it is difficult to imagine that there is not a more material fact than that a proposed treatment's—in this case, an OLU's—safety and efficacy have not been established.

Second, people have the right not to be made the subjects of medical experiments—in this case, not to be prescribed untested OLU—unless they know about and have the capacity to acquiesce to their inherent risks. Protestations to the contrary notwithstanding,<sup>21</sup> this right, well-established internationally since the Nuremberg Trials,<sup>22</sup> is broader than that which applies to “research subjects” as these are currently defined by federal law.<sup>23</sup> That is, federal law does not consider unsupported OLU to be “research” when they are the result of a treating physician’s prescription,<sup>24</sup> whereas the same OLU are “research” when they are the result of a principal investigator’s prescription.<sup>25</sup> Leaving this federal regulatory wordplay aside, there can

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precedent for “the proposition that a physician must disclose to the patient all information that a reasonable person would need to make his or her decision of whether to undergo the procedure” and that “the standard for determining what information must be disclosed by a physician in Maryland is whether a reasonable person in the patient’s position would consider the data significant to the decision whether to submit to a particular treatment or procedure” (internal quotation marks omitted) (citing *Reed v. Campagnolo*, 630 A.2d 1145, 1152 (Md. 1993), and *Wachter v. United States*, 877 F.2d 257, 260 (4th Cir. 1989)).

20 See *infra* notes 78–85 and accompanying text (discussing this case law and noting that, in these cases, the courts themselves may not have been aware that many OLU are unsupported by evidence of safety and efficacy and thus that in some circumstances, a drug’s FDA status may in fact be quite material to the patient’s informed decision). Compare Beck & Azari, *supra* note 11, at 71–72 (arguing that the FDA status of a drug is not material to a patient’s medical decisionmaking and thus does not have to be disclosed), with Johns, *supra* note 9, at 967–71 (arguing the contrary). Beck and Azari’s is the most prominently cited article on this issue, but even they agree that the underlying facts about risk and efficacy are often material ones; the only debatable issue, therefore, is whether (in their terms) FDA status is an appropriate “proxy” for safety and efficacy. See Beck & Azari, *supra* note 11, at 72.

21 See, e.g., Beck & Azari, *supra* note 11, at 72 (arguing that forcing physicians to disclose “FDA regulatory status . . . would confound patient decisionmaking” and is not necessary to meeting informed consent requirements).

22 See Robert D. Mulford, Note, *Experimentation on Human Beings*, 20 STAN. L. REV. 99, 102 (1967) (noting that “[t]he concept of informed consent is central to any standard regulating research on human beings” and that it “was most strongly articulated” in the Nuremberg Code).

23 See *infra* notes 47–48 and accompanying text (setting out related definitions).

24 This is because the regulation of medical practice has—for the most part—remained outside of the federal government’s regulatory jurisdiction. See *infra* Part I.A–B.

25 This is because the federal government has chosen to assume jurisdiction in this different context. See *infra* notes 77–81 and accompanying text (providing an example from the case law).

be no doubt that problematic OLU are experimental in the general sense of that word, and thus that patients are subject to experimental treatment without their knowledge when their physicians fail to disclose the relevant facts in advance.<sup>26</sup> Indeed, proponents of unregulated OLU are otherwise generally forthcoming in describing their motivation as assuring that this important avenue for “innovation” remains unfettered.<sup>27</sup>

Beyond the individual patient, problematic OLU also cause harm to society in the form of unnecessary increases in health care spending. Drugs are prescribed with little or no evidence that they will work; the waste inherent in this effort is compounded if the built-in delays (in securing effective treatment) result in increased costs of care.<sup>28</sup> Drugs are also prescribed for pseudodiseases, illnesses that are poorly defined, thus causing unwarranted growth in pharmaceutical costs.<sup>29</sup> Finally, dangerous side effects causing physical harm and thus additional medical care are more common with OLU than with drugs used on-label.<sup>30</sup>

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26 See *Off-Label Use*, *supra* note 2 (explaining that the reason “[m]any insurance companies will not pay for” an OLU is because it is considered “‘experimental’ or ‘investigational’”).

27 See, e.g., Salbu, *supra* note 8, at 196–98 (elaborating on this innovations argument); cf. Christopher, *supra* note 5, at 247 (noting that, in general, “[t]he medical community argues that overregulation chills innovation and reduces medicine to ‘cookbook’ therapy”).

28 See Dustin D. French et al., Letter to the Editor, *How Well Do Psychotropic Medications Match Mental Health Diagnoses? A National View of Potential Off-Label Prescribing in VHA Nursing Homes*, 36 *AGE & AGEING* 107, 107–08 (2007); Kolata, *supra* note 16.

29 See Daria J. O’Reilly et al., *The Unintended (and Costly) Effects Due to the Introduction of an Unrestricted Reimbursement Policy for Atypical Antipsychotic Medications in a Canadian Public Prescription Drug Program: 1996/97 to 2005/06*, 16 *CANADIAN J. CLINICAL PHARMACOLOGY* 346, 352 (2009).

30 See A.P. Jonville-Béra et al., *Are Incorrectly Used Drugs More Frequently Involved in Adverse Drug Reactions? A Prospective Study*, 61 *EUR. J. CLINICAL PHARMACOLOGY* 232, 235 (2005) (finding that off-label uses cause adverse drug reactions); Elin Kimland et al., *Drug Related Problems and Off-Label Drug Treatment in Children as Seen at a Drug Information Centre*, 166 *EUR. J. PEDIATRICS* 527, 527–28, 531 (2007) (“Adverse drug reactions [are] often associated with *off-label* drug treatment . . .”). An argument to the contrary is that permitting OLU is good “cost-containment” because it does not require society to incur the costs of expensive “FDA approval procedures.” See Salbu, *supra* note 8, at 195. This argument essentially provides that because ascertaining safety and efficacy is expensive, the project ought not (at least in some circumstances) be undertaken. Or, more specifically, it is that pharmaceutical companies ought not be made to bear the financial burdens of ascertaining the safety and efficacy of all of the uses to which their products will be put, including the uses they specifically promote. This argument is only valid if individuals and society are willing to bear the costs associated with unsafe and ineffective drugs.



In this Article, we argue that regulation of physicians' OLU prescribing behavior is warranted to address these harms. Specifically, we argue that when OLU are not justified by high-quality evidence of safety and efficacy, they ought to be appropriately restricted. Notably, this argument excepts OLU that are evidence-based, because these are equivalent to FDA-approved uses. Many drug uses fit into this category and are, as a result, appropriately established as the relevant standard of care.<sup>31</sup>

The argument that problematic OLU ought to be regulated is not new or controversial. Against the consistent refrain that, in the interests of preserving this avenue of medical innovation, all OLU ought to remain unregulated,<sup>32</sup> scholars and policymakers have long urged regulation to protect patients' interests in this context. In the modern context, this latter view has been part of the more general movement toward "evidence-based medicine" and away from treatment approaches that lack evidentiary support.<sup>33</sup> The problem is that regu-

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31 There are a number of instances that meet these criteria. For example, the chemotherapy drug daunorubicin is FDA approved "for remission induction in acute nonlymphocytic leukemia (myelogenous, monocytic, erythroid) of adults," *Cerubidine (Daunorubicin Hydrochloride) Injection, Powder, for Solution* [Bedford Laboratories], DAILYMED, <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=5821#nmlm34067-9> (last revised Nov. 2007), but is also a mainstay of treatment for the analogous disease in children. See I.M. Hann et al., *MRC Trials in Childhood Acute Myeloid Leukemia*, 83 ANNALS HEMATOLOGY S108, S108–12 (Feb. Supp. 2004).

32 See *supra* notes 21–25 and accompanying text (noting this argument).

33 Much of the argument of this Article relies on the use of the term "evidence-based medicine" as the platform from which the evaluation of the efficacy, safety, and utility of any therapeutic must be derived. Although it may be intuitively obvious that physicians would make decisions and clinical recommendations using the best available data to justify the action chosen, it has not been (and is not) always the case. Indeed, it is only in the last twenty years or so that academic medicine has formalized processes to teach students how to approach, find, and evaluate the relevant medical literature that forms the scientific grounding of modern medical practice. The origin of both the term "evidence-based medicine" and the approach it designates is somewhat vague, but appears to have emerged in the early 1990s. See Jeffrey A. Claridge & Timothy C. Fabian, *History and Development of Evidence-Based Medicine*, 29 WORLD J. SURGERY 547, 547 (2005); Gordon H. Guyatt et al., *Users' Guides to the Medical Literature: II. How to Use an Article About Therapy or Prevention: Are the Results of the Study Valid?*, 270 JAMA 2598, 2598–2601 (1993); Andrew D. Oxman et al., *Users' Guides to the Medical Literature: I. How to Get Started*, 270 JAMA 2093, 2093–95 (1993). David L. Sackett, in an influential editorial in the *British Medical Journal*, defined the term as follows:

Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. . . . By best available external clinical evidence we mean clinically relevant research, often from the basic sciences of medicine, but especially from patient centred clinical research into the accuracy and precision of

latory approaches to date have not and, without more, likely cannot solve the problem. Indeed, even if this is a matter of balancing the interest in innovation against the interest in protecting patients' welfare otherwise, a new approach is necessary.

The favorite target of regulators, restriction of pharmaceutical companies' promotion of problematic OLU,<sup>34</sup> has been only marginally effective. This is due, at least in part, to the fact that the companies' incentives are almost entirely in the other direction: their financial gains are directly related to the extent to which their products are used, experimentally or not, off-label.<sup>35</sup> The most recent twists on this old regulatory approach are unlikely to work because they do nothing to alter these incentives. Indeed, to the contrary, they were developed with the understanding that pharmaceutical companies would inevitably continue to find ways to market OLU, and with the hope that if this marketing could be controlled—specifically by permitting the marketing only of OLU with third-party evidence of safety and efficacy—patients' welfare would be better protected.<sup>36</sup> Recent revelations that pharmaceutical companies are paying third parties to claim authorship of articles submitted to peer-reviewed jour-

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diagnostic tests (including the clinical examination), the power of prognostic markers, and the efficacy and safety of therapeutic, rehabilitative, and preventive regimens. External clinical evidence both invalidates previously accepted diagnostic tests and treatments and replaces them with new ones that are more powerful, more accurate, more efficacious, and safer.

David L. Sackett et al., Editorial, *Evidence Based Medicine: What It Is and What It Isn't*, 312 *BRIT. MED. J.* 71, 71–72 (1996). Currently, coursework, lectures, and the like constitute components of the curricula of most, if not all, medical schools in the United States, and formal training in evidence-based data collection, analysis, and implementation is required by both the American Boards of Internal Medicine and Pediatrics. See, e.g., David B. Rueben, *Chair's Message*, AM. BOARD INTERNAL MED., <http://abim.org/about/board-of-directors/chairs-message.aspx> (last visited Feb. 15, 2011) (stating that the board is focusing on data collection and evidence-based medicine). Thus, it is fair to say that American physicians should be expected to be expert arbiters of the available scientific literature evidence base (or lack of it) in supporting any particular therapeutic modality.

34 See *supra* note 6 and accompanying text.

35 As one commentator noted, “Companies regard the risk of multimillion-dollar penalties [in this context] as just another cost of doing business.” Evans, *supra* note 13. Specifically, “[a]s large as the penalties are for drug companies caught breaking the off-label law, the fines are tiny compared with the firms' annual revenues.” *Id.* For example, “[t]he \$2.3 billion in fines and penalties Pfizer paid for marketing Bextra and three other drugs . . . amount to just 14 percent of its \$16.8 billion in revenue from selling those medicines from 2001 to 2008.” *Id.*

36 See *infra* Part II.A (setting out this argument).

nals that are actually ghost written by company contractors<sup>37</sup> lay bare the fundamental flaw in this strategy: one can keep hoping and (more pragmatically) fining the companies, but so long as the profits to be made from unlawful marketing of OLU outweigh those fines, it is rational for the companies to write them off as part of the cost of doing business.

At least in part for this reason, commentators who continue to be concerned about the implications of problematic OLU have renewed older calls for nonbinding professional standards to govern physicians' prescribing behavior.<sup>38</sup> This latter step is particularly important, because it signals the recognition that a comprehensive strategy regulating all relevant actors, or else a targeted strategy focusing on the physician-patient relationship, is more likely to be effective than one focusing exclusively on manufacturers. Proposals to regulate physicians' OLU, even if only through nonbinding professional standards, also reflect the recognition that physicians share responsibility for their implications. The problem with this alternative approach is that nonbinding standards often go unheeded. This is perhaps especially true in circumstances where the audience is, as physicians are, inculcated in a culture that has long viewed professional independence as normative.<sup>39</sup>

It is for these reasons that we argue in this Article on behalf of binding legal regulation of physicians' related prescribing behavior. Such regulation is likely to be effective because physicians are the most immediate link between drugs and the patients who would take them; in legal parlance, unlike pharmaceutical companies, physicians

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37 See Jeffrey R. Lacasse & Jonathan Leo, *Ghostwriting at Elite Academic Medical Centers in the United States*, PLoS MED., Feb. 2010, <http://www.plosmedicine.org/article/info:doi%2F10.1371%2Fjournal.pmed.1000230>; Stephanie Saul, *Merck Wrote Drug Studies for Doctors*, N.Y. TIMES, Apr. 16, 2008, at C1; Natasha Singer, *Medical Papers by Ghostwriters Pushed Therapy*, N.Y. TIMES, Aug. 5, 2009, at A1.

38 See Dresser & Frader, *supra* note 5. This call revives an earlier theme in the literature. See Arthur S. Levine, *Clinical Trials and the Community Physician*, 51 *CANCER* 2498, 2498–2502 (1983) (addressing and promoting the introduction of protocols in community hospitals for testing new therapeutic techniques); Robert J. Levine, *The Boundaries Between Biomedical or Behavioral Research and the Accepted and Routine Practice of Medicine*, in NAT'L COMM'N FOR THE PROT. OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, *THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH* app. I, at 1-1 to 1-44 (1978) [hereinafter *THE BELMONT REPORT*]; *Legal Implications of the Boundaries Between Biomedical Research Involving Human Subjects and the Accepted or Routine Practice of Medicine*, in *THE BELMONT REPORT*, *supra*, app. II, at 16-44 to 16-45.

39 See Celia Davies, Editorial, *Getting Health Professionals to Work Together*, 320 *BRIT. MED. J.* 1021, 1021–22 (2000) (discussing research displaying the need for more collaboration on the part of doctors and hospital staff).

are the “direct cause” of patients’ OLU. Regulating physicians is also likely to be effective because their incentives are fundamentally different from those that guide pharmaceutical companies. That is, physicians’ bottom line is not generally tied to the number and amount of OLU they “sell” by prescription. Rather, it is tied to doing right by their patients, and, consequently, to their professional reputations.

In contrast with the widely held view that pharmaceutical companies’ promotion of problematic OLU ought to be regulated, our argument to regulate physicians’ promotion (by prescription) of these same OLU is new and it will be controversial. This society has a strong tradition of deference to physicians’ autonomy and judgment in the context of the physician-patient relationship. It is generally held that it is in the interests of patients for the physicians who know them best to be able to make unfettered treatment decisions, including resorting to innovative therapy when the circumstances require. Physicians’ right to make unregulated treatment decisions is intended, at least in part, to protect patients’ right to use whatever treatment they wish and, relatedly, to decide in the privacy of the physician-patient relationship what this treatment should be.<sup>40</sup> These views are so strongly held that physicians’ prescribing practices, both in general, and with respect to OLU in particular, have never been effectively regulated.<sup>41</sup> To the contrary, the prevailing *laissez-faire* approach suggests that even discussing such regulation is taboo.<sup>42</sup>

It is essential that physicians retain substantial freedom to exercise judgment and even, when necessary, to innovate in their patients’ best interests. However, we disagree that absolutely unfettered physician liberty is a necessary or appropriate way to achieve these ends. Even our most fundamental individual liberties—those described in the Bill of Rights, including parental autonomy, religious freedom, the sanctity of the home, and so on—are restricted and violable in certain circumstances. Since it is patients’ best interests that justify physicians’ liberty in the first instance, their interests must also be an appropriate basis for restrictions on that liberty. More specifically, it is an anachronism in this modern era of evidence-based medicine to

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40 See generally Edmund D. Pellegrino, *Patient and Physician Autonomy: Conflicting Rights and Obligations in the Physician-Patient Relationship*, 10 J. CONTEMP. HEALTH L. & POL’Y 47, 58–63 (1994) (discussing physicians’ traditional discretion).

41 See *infra* Part I (describing the dearth of effective regulation in additional detail).

42 See, e.g., Christopher, *supra* note 5, at 247 (noting that “physicians attack some attempts to regulate medicine with the vigor of an artist resisting censorship” and that “[t]he medical community argues that overregulation chills innovation and reduces medicine to ‘cookbook’ therapy”).

suggest that physicians ought to be unrestricted as they engage in innovation; innovation is, after all, simply a euphemism for experimentation, however well intended. To suggest that physicians are not required to inform their patients that they are innovating as they treat is particularly anathema.

To argue that physicians' OLU-prescribing behavior ought to be legally regulated in the interests of their patients is only to begin the discussion. The nature of the restrictions, the identity of the regulator(s), and appropriate penalties for violations, if any, all need to be addressed. We do not propose a particular "best solution" in this Article; to do so would be premature given this society's long and largely unaltered history of deference to physicians' good faith and judgment. Rather, our project is primarily to make the case for legal regulation, with a view toward initiating what we hope will be a new and serious discussion of the possibilities for and advantages and disadvantages of particular approaches.

To these ends, Part I describes the existing regulatory landscape, Part II makes the case for binding legal regulation of physicians' OLU-prescribing behavior, and Part III provides a framework for next steps, including a discussion of the necessary elements of a sound regulatory regime and possible institutional approaches. The Article concludes that although the physician-patient relationship is sacrosanct, it cannot be privileged at the expense of the welfare of the very individuals it is designed to protect. Providing for careful and meaningful restrictions on physicians' OLU-prescribing behavior ultimately strikes a better balance among the relevant interests than does the "laissez-faire" approach that prevails today.

## I. EXISTING TREATMENT OF PHYSICIANS' OLU

The prevalence of OLU in medical practice is often noted and well understood, at least within the relevant professional communities. More obscure is that OLU, including physicians' OLU, are effectively unregulated. This regulatory vacuum is the result of the federal government's decision to leave to the states the regulation of medical practice within their borders; the states' decision generally to defer to the medical profession, allowing it substantially to self-regulate; and the medical profession's decision with respect to OLU in particular to suggest a nonbinding gold standard of evidence-based medicine, which has the effect of recommending but not mandating any particular prescribing behavior. Those who study this area understand the larger implications of these individual deferences. However, it is

often the case that even knowledgeable decisionmakers believe that they do not need to regulate because someone else is doing this work.

### A. *The Federal Government*

There are two federal institutions with related jurisdiction: the Food and Drug Administration (FDA) and the National Institutes of Health (NIH). Neither regulates physicians' OLU.

The FDA was established in the early twentieth century to regulate purveyors of false and harmful elixirs: in other words, (bad) drug manufacturers and distributors.<sup>43</sup> It was never intended to regulate physicians or the drugs' ultimate consumers; indeed, the doctor-patient relationship in particular has always been considered off limits by the federal government for regulatory purposes.<sup>44</sup> The FDA is responsible for authorizing manufacturers to conduct clinical trials of experimental drugs, for approving drugs for specific uses where those uses have been found to be safe and effective after clinical trials, for approving the labels and marketing materials that accompany approved drugs once they are distributed in the marketplace, and for sanctioning drug companies when they are found to have improperly promoted unapproved (including off-label) uses of their products. The FDA's actions do affect physicians' and patients' choices when it allows or disallows the distribution of particular products by their

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43 See Veronica Henry, *Problems with Pharmaceutical Regulation in the United States*, 14 J. LEGAL MED. 617, 618–20 (1993); Katherine A. Helm, Note, *Protecting Public Health from Outside the Physician's Office: A Century of FDA Regulation from Drug Safety Labeling to Off-Label Drug Promotion*, 18 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 117, 125 (2007).

44 See Salbu, *supra* note 8, at 190–91. As one court recently wrote with respect to OLU in particular,

[t]he FDA has always recognized that the [Food, Drug, and Cosmetics] Act does not . . . limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may choose to prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. The FDA also observes that accepted medical practice often include[s] drug use that is not reflected in approved drug labeling.

Blazoski v. Cook, 787 A.2d 910, 919 (N.J. Super. Ct. App. Div. 2002) (first alteration in original) (quoting *Morlino v. Med. Ctr. of Ocean Cnty.*, 706 A.2d 721, 730 (N.J. 1998)); see also *id.* at 918 (“[O]ff-label’ usage of medical devices ‘is an accepted and necessary corollary of the FDA’s mission to regulate in this area without directly interfering with the practice of medicine.’” (alteration in original) (quoting *Buckman Co. v. Plaintiffs’ Legal Comm.*, 531 U.S. 341, 350 (2001))). The two exceptions to this rule are clinical trials with patient/subjects, see 21 C.F.R. § 50 (2010); *id.* § 56; 45 C.F.R. § 46 (2010), and the regulation of narcotics, amphetamines, and hallucinogens, see Controlled Substances Act, 21 U.S.C. §§ 801–904 (2006).

manufacturers, or when it requires aftermarket revisions (including warnings) to physician package inserts,<sup>45</sup> but the effect is only indirect.

One could understand OLU as a form of clinical research, especially those situations in which the OLU is innovative or lacks a firm evidentiary base of support. In these cases OLU could fall under the regulatory umbrella of the NIH. The NIH's Office of Human Subjects Research (OHSR) is responsible for the regulation of "human subjects research," and local Institutional Review Boards (IRBs) are charged with the application and implementation of these policies and regulations to ensure both the safety of the subjects and the integrity of the experiments in which they are taking part.<sup>46</sup> "Human subjects research" is a statutory term of art that "means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."<sup>47</sup> This is both intentionally and expressly a narrow conception of research. As the Code of Federal Regulations states:

*Research subject to regulation*, and similar terms are intended to encompass those research activities for which a federal department or agency has specific responsibility for regulating as a research activity, (for example, Investigational New Drug requirements administered by the Food and Drug Administration). It does not include research activities which are incidentally regulated by a federal department or agency solely as part of the department's or agency's broader responsibility to regulate certain types of activities whether research or non-research in nature . . . .<sup>48</sup>

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45 See *infra* notes 72–77 and accompanying text (discussing the effects of such aftermarket actions on medical malpractice actions).

46 See 45 C.F.R. § 46.102(g)–(j) (defining Institutional Review Boards and their approval process); Office of Human Subjects Research, *OHSR Information Sheets/Forms*, NAT'L INSTS. HEALTH (Nov. 20, 2006), <http://ohsr.od.nih.gov/info/sheet1.html> (discussing the OHSR's responsibilities).

47 See 45 C.F.R. § 46.102(d). A "human subject" for purposes of this policy is defined as "a living individual about whom an investigator (whether professional or student) conducting research obtains (1) [d]ata through intervention or interaction with the individual, or (2) [i]dentifiable private information." *Id.* § 46.102(f). "[G]eneralizable knowledge" is "knowledge related to health that can be applied to populations outside the population being studied. That is, participants in a research project may or may not benefit directly from the study, but a larger group is expected to gain from the knowledge obtained in the study." *102.2 Organizational Policy on the Definition of Research as It Applies to Clinical Practice and Public Health Activities*, JOHNS HOPKINS MED. (Sept. 2007), [http://www.hopkinsmedicine.org/institutional\\_review\\_board/guidelines\\_policies/organization\\_policies/102\\_2.html](http://www.hopkinsmedicine.org/institutional_review_board/guidelines_policies/organization_policies/102_2.html).

48 45 C.F.R. § 46.102(e).

By definition, the term “human subjects research” also does not include research, experimental, and innovative activities involving human subjects that are entirely outside of the purview of the federal government.<sup>49</sup>

Because IRBs and the OHSR have never considered even experimental or innovative OLU to be “human subjects research,” these institutions have never sought to govern physicians’ related prescribing.<sup>50</sup> There are several explanations for this, including primarily that the doctor-patient relationship is involved and, as we have already explained, this relationship is generally considered to be off limits to federal regulators.<sup>51</sup> Relatedly, aside from a few quite famous historical examples of doctors using their patients or others to obtain generalizable knowledge,<sup>52</sup> the doctor-patient relationship—typically characterized by the intent of the physician to cure or alleviate the individual patient’s condition using either established or innovative approaches—has not *looked* like that which these institutions were charged with regulating.<sup>53</sup> Thus, even when a physician’s OLU could be considered to be entirely experimental,<sup>54</sup> the fact that it is directed at a patient who, it is at least hoped, may be helped by the treatment is sufficient to take it out of the purview of IRBs and the OHSR. There are no other federal agencies with relevant jurisdiction.

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49 In addition to OLU, well-known examples of experimental or innovative activity that falls outside of the jurisdiction of the OHSR include some types of stem cell and recombinant DNA research. *See id.* § 46.101(a)–(i) (describing research to which this policy applies). However, all clinical research using human subjects is regulated by the OHSR, no matter what the funding source (private or government). *See id.* § 46.101(a).

50 *See supra* notes 47–49 (distinguishing “human subjects research” from innovative medical practice on the basis that the former is to obtain generalizable knowledge and the latter is to cure or alleviate an individual patient’s condition).

51 *See supra* note 42.

52 *See, e.g.,* Doriane Lambelet Coleman, *The Legal Ethics of Pediatric Research*, 57 DUKE L.J. 517, 530–31 (2007) (describing experiments on children as patients).

53 Physician-patient relationships that involve, in addition to diagnosis and treatment, formal enrollment of the patients in studies designed to test the merits of OLU are the exception to this proposition. These patients and their physicians acting as investigators are subject to the federal regulations governing human subjects research. *See* 21 C.F.R. § 50.1(a) (2010); *id.* § 56.101; 45 C.F.R. § 46.101(a)–(i). The difference for these patients is that the intent of the studies is not to cure or alleviate their particular symptoms, but rather to gather generalizable knowledge about their condition.

54 Our use of the term “experimental” refers not to a research endeavor, one aimed towards generating knowledge applicable to others, but rather to one in which the outcome is unknown and cannot be predicted with a high degree of confidence.



### B. *The States*

The assumption underlying the federal government's hands-off approach to the physician-patient relationship, and thus to physicians' OLU, is that the regulation of medical practice is mostly a matter of local and professional concern, best left to the states individually to regulate.<sup>55</sup> In general, the states' approach to this deference has been two pronged. First, the states require that physicians practicing within their boundaries be licensed by their medical boards. Second, they have evolved medical malpractice law to compensate patients who are injured by their doctors' negligent care. Neither the licensing requirement nor malpractice law effectively restricts physicians' problematic OLU.

#### 1. The Licensing Requirement

In all fifty states the practice of medicine is authorized and regulated by individual medical boards, which are in turn governed by analogous statutory rules and laws or medical practice acts. Individual state-regulated licensing of physicians was officially sanctioned in 1889 when the U.S. Supreme Court ruled that West Virginia's police power authority to safeguard the public welfare encompassed the right to demand that physicians have certain qualifications of education and skill.<sup>56</sup> This was followed by the landmark *Flexner Report* in 1910, which called for the standardization of medical education and state regulation of medical schools and their graduates.<sup>57</sup> Not only did the so-called for-profit proprietary schools quickly go out of business, leading to a significant contraction in the number of institutions available for medical education, but the curricula of the "survivors" became increasingly uniform, adhering to Flexner's call for a more science-based education, consistent with the rapid emergence of scientific medicine.<sup>58</sup> In 1912, the state medical boards established the Federation of State Medical Boards, an organization that continues to this day to coordinate pre- and postgraduate educational requirements,

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<sup>55</sup> See *supra* note 41 and accompanying text.

<sup>56</sup> *Dent v. West Virginia*, 129 U.S. 114, 121–23 (1889). The Court also held that such a licensing requirement could not be construed as a restraint of trade. *Id.*

<sup>57</sup> See ABRAHAM FLEXNER, *MEDICAL EDUCATION IN THE UNITED STATES AND CANADA passim* (1910); Andrew H. Beck, *The Flexner Report and the Standardization of American Medical Education*, 291 *JAMA* 2139, 2139–40 (2004).

<sup>58</sup> Indeed, this was probably the first official endorsement of "evidence-based medicine." See *supra* note 33.

and ongoing skill and continuing medical educational assessments for practicing physicians.<sup>59</sup>

To receive a medical license, a physician must not only graduate from an accredited medical school, but she must also pass a three-part examination, complete postgraduate clinical training from an accredited hospital residency program, and be judged to be of "good character." Further, licenses are renewed periodically (in the authors' state of North Carolina, there is annual renewal<sup>60</sup>) in which physicians must present evidence of their continued ability to practice high-quality and ethical medicine, including their accumulation of designated numbers of continuing education credits in their field. However, there is no microexamination of *how* they practice or their philosophical approach to pharmaceutical prescribing. Thus, the medical licensing boards are not well placed either to regulate or even investigate anything other than the most grievous violations of medical standards, generally brought to their attention by disgruntled or poorly served patients, or occasionally by law enforcement authorities. Although the boards have the authority to suspend, limit, or even permanently revoke a doctor's license for a wide variety of violations of law or standards of practice, they tend to grant great leeway to physicians in the way they care for their patients and prescribe medicines.<sup>61</sup> Since federal law, state medical practice statutes, and professional codes of ethics do not aim to regulate the private practice of medicine (except within the broad boundaries just described), scrutiny of off-label use is generally off limits.<sup>62</sup>

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59 See *FSMB Mission & Goals*, FED'N STATE MED. BOARDS, <http://www.fsmb.org/mission.html> (last visited Feb. 12, 2011); *FSMB History*, FED'N STATE MED. BOARDS, <http://www.fsmb.org/history.html> (last visited Feb. 12, 2011); *Policy Documents*, FED'N STATE MED. BOARDS, [http://www.fsmb.org/grpol\\_policydocs.html](http://www.fsmb.org/grpol_policydocs.html) (last visited Feb. 12, 2011).

60 See *Continuing Medical Education (CME) FAQs*, N.C. MED. BOARD, [http://ncmedboard.org/faqs/list/category/continuing\\_medical\\_education\\_cme](http://ncmedboard.org/faqs/list/category/continuing_medical_education_cme) (last visited Feb. 12, 2011).

61 See *State of the States: Physician Regulation 2009*, FED'N STATE MED. BOARDS, 6, [http://www.fsmb.org/pdf/2009\\_state\\_of\\_states.pdf](http://www.fsmb.org/pdf/2009_state_of_states.pdf) (last visited Feb. 12, 2011) ("While medical boards sometimes find it necessary to suspend or revoke licenses, regulators have found many problems can be resolved with additional education or training in appropriate areas. . . . This compromise protects the public while maintaining a valuable community resource in the physician.").

62 For information on licensure requirements, see *Becoming a Physician: Medical Licensure*, AM. MED. ASS'N, <http://www.ama-assn.org/ama/pub/education-careers/becoming-physician/medical-licensure.shtml> (last visited Feb. 12, 2011).

## 2. Medical Malpractice Law

Medical malpractice law sets enforceable standards of practice and provides meaningful sanctions for violation of those standards. However, this law is particularly ineffective as a regulatory mechanism for physicians' OLU. This is specifically in contrast to the law's effectiveness in regulating physicians' competence in other respects, including standards of care in evaluating patients, conducting procedures, and meeting informed consent obligations. The ineffectiveness of medical malpractice law as a tool to regulate physicians' OLU has everything to do with yet a second deference—this time by the states' judiciaries, which administer this law—to physicians' collective and individual judgments. This particular deference is not surprising, as medical malpractice law in general reflects the standard of care as set by the medical profession, not by the judiciary or juries.<sup>63</sup> There is no indication that proposals for tort reform or medical malpractice reform include mandates to the legislatures to alter this deferential approach.

The best indication of the ineffectiveness of medical malpractice law as a tool to regulate OLU is probably the dearth of published cases, either reported (useful as precedent in future cases) or unreported (officially unavailable as precedent) in which off-label use by a medical provider was a focus of the plaintiff's case. Furthermore, the substance of the published decisions reinforces the suggestion from the numbers that off-label prescribing is a weak basis for finding liability against a physician. Specifically, state courts over the past ten years have published approximately thirty such decisions, only a very few of which can be interpreted as restrictive of physicians' off-label practices.<sup>64</sup> Although this may not represent all of the cases filed—for

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63 See DAN B. DOBBS, *THE LAW OF TORTS* 633 (2001). As Professor Dobbs explains:

The standard of care is not the reasonable person standard used in most negligence cases. The reasonable person standard asks the trier to weigh the reasonableness, that is at least in part to weigh the risks and utilities of the defendant's conduct; but the professional standard asks the trier only to determine whether the defendant's conduct conformed to the medical standard or medical custom in the relevant community. Thus under the traditional rule, as long as a doctor follows the medical standard or custom, he is not negligent, regardless of how risky the custom or how unnecessary.

*Id.*

64 This number is the result of a Westlaw search in February 2010 according to the following criteria: the database was "allstates" and the search terms were "medical w/1 malpractice & off w/1 label." The same result was obtained when the search terms were changed to "medical w/1 malpractice & off-label." The cases that we describe as arguably restrictive of physicians' off-label practices are those described in

example, some may have settled and some decisions may not have been published—the small number strongly suggests the weakness of this legal theory as a litigation strategy. Medical malpractice law is only effective as regulation if plaintiffs' lawyers are willing to bring cases, and the contingency fee system assures that, in the main, they will be unwilling to bring cases that are unlikely to be successful.

Most important is that the cases evidence strong deference to the professional judgment of individual physicians. Indeed, to the extent that a reliable generalization is possible from the relatively small number of cases, it is that the law is even more solicitous of physicians' right to exercise independent professional judgment about what their patients need, including when to use particular drugs, than the relevant American Medical Association (AMA) policy. Specifically, where that policy confirms physicians' right to use drugs off-label when such use is based on "sound scientific evidence and . . . medical opinion"<sup>65</sup>—in other words, when it is consistent with evidence-based medicine—and recommends particular compendia and the peer-reviewed literature in this regard, the law suggests that they can deviate from that policy when, exercising the "degree of skill and proficiency which is commonly experienced by the ordinary, skillful, careful and prudent physician,"<sup>66</sup> they determine that their patients could benefit from different treatment.<sup>67</sup> As the Supreme Court of Missouri recently held in a case against a doctor who used chelation therapy to treat patients with vascular conditions contrary to a specific AMA policy that identified its use in this context as "an experimental process without proven efficacy,"<sup>68</sup>

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notes 67–72 and accompanying text. These involve the decision of some courts to permit malpractice plaintiffs to introduce physician package inserts into evidence to establish the standard of care.

65 *H-120.988 Patient Access to Treatments Prescribed by Their Physicians*, AM. MED. ASS'N, <https://ssl3.ama-assn.org/apps/ecomm/PolicyFinderForm.pl?site=www.ama-assn.org&uri=/amal/pub/upload/mm/PolicyFinder/policyfiles/HnE/H-120.988.HTM> (last visited Feb. 12, 2011).

66 *See Silberstein v. Berwald*, 460 S.W.2d 707, 709 (Mo. 1970).

67 *See, e.g., State Bd. of Registration for the Healing Arts v. McDonagh*, 123 S.W.3d 146, 164 (Mo. 2003) (noting in the context of a case challenging a physician's off-label use of chelation therapy that "[p]hysicians are afforded considerable leeway in the use of professional judgment to decide on appropriate treatments, especially when applying the negligence standard. For instance, [another] medical negligence case, holds that 'as long as there is room for an honest difference of opinion among competent physicians, a physician who uses his own best judgment cannot be convicted of negligence, even though it may afterward develop that he was mistaken.'" (quoting *Haase v. Garfinkel*, 418 S.W.2d. 108, 114 (Mo. 1967))).

68 *See id.* at 150 (quoting from the AMA's position statement on the off-label use of chelation therapy, which also included the admonitions that "(1) [t]here is no

[a]pplication of this standard does not merely require a determination of what treatment is most popular [among members of the medical profession or the medical specialization in question.] Were that the only determinant of skill and learning, any physician who used a medicine for off-label purposes, or who pursued unconventional courses of treatment, could be found to have etngaged in . . . negligence . . . .<sup>69</sup>

In other words, the AMA policy suggests an aspirational standard of care: that before physicians give their patients drugs off-label, some sort of experimenting has to have been done by someone else so that the compendia and literature already reflect the particular benefits of such use. The law does not contain this restriction.<sup>70</sup>

The AMA's aspirations notwithstanding, the medical profession itself often fails to heed these pronouncements. That is, the medical standard of care—which the law borrows as its standard for purposes of medical malpractice liability—is not a reliable proxy for safety and efficacy because it is based on accepted practice, and accepted practice does not have to be and is often not evidence based.<sup>71</sup> Indeed, if

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scientific documentation that the use of chelation therapy is effective in the treatment of cardiovascular disease, atherosclerosis, rheumatoid arthritis, and cancer; [and] (2) chelation therapy proponents should conduct controlled studies and adhere to FDA research guidelines if they want the therapy to be accepted more broadly” (first alteration in original) (internal quotation marks omitted)); *H-175.994 Chelations Therapy*, AM. MED. ASS'N (2004), <https://ss13.ama-assn.org/apps/ecommm/PolicyFinderform.pl?site=www.ama-assn.org&uri=/ama1/pub/upload/mm/PolicyFinder/policyfiles/HnE/H-175.994.HTM>; see also *Baker v. Smith & Nephew Richards, Inc.*, No. 95-58737, 1999 WL 811334, at \*17 (Tex. Dist. Ct. June 7, 1999) (“Once a device has been cleared for labeling for one use, physicians in their private practice may use it in any manner they deem medically appropriate, including uses being studied pursuant to an IDE.”).

<sup>69</sup> *McDonagh*, 123 S.W.2d at 159.

<sup>70</sup> See *id.* at 165 (noting, in response to the claim that a physician failed to abide by AMA guidelines, that “medicine is not readily regulated by a standard cookbook or set of rules”). The court in *McDonagh* even went so far as to suggest that physicians could properly use a therapy off-label that was generally held to be ineffective so long as it was otherwise harmless and patients could be healed by believing in its curative properties:

Medicine is an art, as well as a science, as its practitioners are taught. It is also a dynamic field, where beliefs about what is conventional therapy can change over time. What is effective treatment is often a combination, not just of art and science, but of belief. The patient may get better if the patient is convinced of the usefulness of the therapy.

*Id.* at 166.

<sup>71</sup> See Philip M. Rosoff, *Can Underpowered Clinical Trials Be Justified?*, IRB: ETHICS HUM. RES., May–June 2004, at 16, 16. The story of bone marrow transplants and breast cancer is illustrative. In 1986 doctors reported using very high doses of chemo-

therapy to eliminate residual cancer in patients with advanced disease and “rescuing” them with using their own bone marrow. The initial, noncontrolled, results were impressive, thus providing proof of principle in terms of both feasibility and potential efficacy. See J. Paul Eder et al., *High-Dose Combination Alkylating Agent Chemotherapy with Autologous Bone Marrow Support for Metastatic Breast Cancer*, 4 J. CLINICAL ONCOLOGY 1592, 1592 (1986); W.P. Peters et al., *High-Dose Combination Alkylating Agents with Autologous Bone Marrow Support: A Phase I Trial*, 4 J. CLINICAL ONCOLOGY 646, 652–53 (1986). The data were impressive enough that others adopted the approach and it became the “standard of care.” Public pressure built to provide this “miracle” therapy to women and have insurance companies pay for it. See RICHARD A. RETTIG ET AL., *FALSE HOPE passim* (2007). This practice was so accepted that a number of patients successfully sued their insurance companies when they were denied coverage for autologous transplantation for breast cancer. See, e.g., *Henderson v. Bodine Aluminum, Inc.*, 70 F.3d 958, 961 (8th Cir. 1995) (granting plaintiff’s requested injunctive relief on the basis that her insurance “plan covers HDCT for other types of cancer for which it is an accepted treatment, and . . . she has shown considerable un rebutted evidence that HDCT is an accepted breast cancer treatment with significantly higher success rates than standard chemotherapy”). Unfortunately, when Phase 3 randomized trials were eventually performed some years later, the results of these trials demonstrated that the benefit of autotransplantation for advanced breast cancer was marginal at best. See Martin S. Tallman et al., *Conventional Adjuvant Chemotherapy with or Without High-Dose Chemotherapy and Autologous Stem-Cell Transplantation in High-Risk Breast Cancer*, 349 NEW ENG. J. MED. 17, 17 (2003); Sjoerd Rodenhuis et al., *High-Dose Chemotherapy with Hematopoietic Stem-Cell Rescue for High-Risk Breast Cancer*, 349 NEW ENG. J. MED. 7, 14–15 (2003); C. Farquhar et al., *High Dose Chemotherapy and Autologous Bone Marrow or Stem Cell Transplantation Versus Conventional Chemotherapy for Women with Metastatic Breast Cancer*, 1 COCHRANE DATABASE SYSTEMATIC REVIEWS., 2005, at 2 (D.O.I.: 10.1002/14651858.CD0031342); Gerald J. Elfenbein, Editorial, *Stem-Cell Transplantation for High-Risk Breast Cancer*, 349 NEW ENG. J. MED. 80, 80–82 (2003); H. Gilbert Welch & Juliana Mogielnicki, *Presumed Benefit: Lessons from the American Experience with Marrow Transplantation for Breast Cancer*, 324 BRIT. MED. J. 1088, 1091–92 (2002). Hence, many thousands of women were treated according to the guiding wisdom of their doctors, hewing to the prescribed guidelines embodied by the accepted wisdom within the standard of care.

The story of rituximab (Rituxan®) is similarly illustrative. This drug is a product of genetic engineering and is FDA approved for use in non-Hodgkin’s lymphoma. See *Rituxan (Nituximab) Injection, Solution [Genentech, Inc.]*, DAILYMED, <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=16017> (last revised Jan. 2010). However, it is now prescribed for a wide variety of unapproved uses. See Richard Imrich et al., *Autoimmune Autonomic Ganglionopathy: Treatment by Plasma Exchanges and Rituximab*, 19 CLINICAL AUTONOMIC RES. 259, 259–62 (2009); A.Ø. Jensen et al., *Treatment of Treatment-Resistant Autoimmune Blistering Skin Disorders with Rituximab*, 160 BRIT. J. DERMATOLOGY 1359, 1359–61 (2009); C. Lebrun et al., *Successful Treatment of Refractory Generalized Myasthenia Gravis with Rituximab*, 16 EUR. J. NEUROLOGY 246, 246–49 (2009); Brigitta U. Mueller et al., *One Year Follow-Up of Children and Adolescents with Chronic Immune Thrombocytopenic Purpura (ITP) Treated with Rituximab*, 52 PEDIATRIC BLOOD CANCER 259, 259–61 (2009); V. Torrente-Segarra et al., *Clinical, Biological and Ultrasonographic Remission in a Patient with Musculoskeletal Systemic Lupus Erythematosus with Rituximab*, 18 LUPUS 270, 270–72 (2009). There have been several alerts from the

it were required either by the medical profession itself or by law that the accepted practice be evidence based, many patients, including some children and individuals with rare or unusual diseases, would receive no treatment at all.<sup>72</sup>

In any event, to the extent that some (but not all) states' case law suggests anything that could be considered restrictive of physicians' OLU, it is only in the requirement that, when treating patients, providers must take account of relevant information from physician package inserts, also included in the *Physician's Desk Reference* (PDR), about proper product use (in the context of medical devices) and (in the case of medical devices and drugs) contraindications, including those discovered aftermarket and set out in amended product labels.<sup>73</sup> Notably, however, the requirement is merely that medical providers take this information into account, not that they tailor their uses based on it regardless of the circumstances otherwise. Thus, in jurisdictions that adhere to this approach, physician package inserts proffered by the plaintiff-patients are admissible as evidence of the standard of care so long as they are accompanied by expert testimony supporting this claim.<sup>74</sup> Defendant-doctors who can muster evidence that the physician package inserts do not reflect the standard of care—for example, evidence that in the unique circumstances pertinent to the care of a specific patient, the information in the package inserts was inapplicable, outweighed by other factors, or that there were other acceptable approaches—will be found not liable.

Jurisdictions that reject this approach do not permit plaintiff-patients to introduce package inserts as evidence of the standard of care because they believe that juries could be misled by the negative

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FDA after reports of severe and occasionally fatal reactions to this drug, finally resulting in a so-called "black box" warning (added to the required drug information package insert data sheet). Most of these warnings came after unexpected side effects occurred in patients receiving rituximab for OLU. See *Rituximab (Marketed as Rituxan) Information: FDA Alert [12/18/2006]*, <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm109106.htm> (last updated Jan. 21, 2010).

<sup>72</sup> See *supra* note 31 and accompanying text.

<sup>73</sup> See, e.g., *Richardson v. Miller*, 44 S.W.3d 1, 15–17 (Tenn. Ct. App. 2000) ("The great weight of authority is that a drug's labeling or its parallel PDR reference is admissible, as long as it is accompanied by other expert evidence regarding the standard of care."). This requirement has been established indirectly, as a result of the evidentiary value of package inserts to establish the standard of care. This point is discussed in additional detail in the text.

<sup>74</sup> See *id.*

implication that OLU are necessarily inappropriate.<sup>75</sup> As one court recently explained:

[I]f we were to allow the package insert into evidence . . . , the jury would be allowed to consider the statements in the insert for the truth of what they assert: that there is only one way to use the [drug or device]. In an age where drugs are frequently used for purposes not approved by the FDA, we decline to set such a precedent. . . . [W]e understand package inserts for pharmaceuticals and medical devices to represent recommendations by the manufacturer, not comprehensive instruction as to the use of the drug or device.<sup>76</sup>

In such jurisdictions medical providers are not required by malpractice law to take the information contained in package inserts into account except to the extent that this information otherwise reflects the standard of care.<sup>77</sup>

Not only does malpractice law permit medical providers substantial freedom to use drugs off-label and as they see fit, it also permits them to make this choice without informing their patients that the use is off-label.<sup>78</sup> The case law involving informed consent claims based in off-label prescribing is also very sparse, and most of it relates to the off-label use of devices rather than drugs. However, to the extent that this case law is probative, it suggests that—regardless of the nature and extent of the evidentiary support for a particular use—off-label status is not material to patients' ability to make informed decisions about their options. This notwithstanding that “[t]he test for determining whether a particular risk must be disclosed is its materiality to

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<sup>75</sup> See *Arnold v. Lee*, 720 N.W.2d 194, 2006 WL 1410161, at \*6 (Iowa Ct. App. May 24, 2006) (unpublished table decision) (upholding district court's refusal to admit package insert into evidence because of the “risk for unfair prejudice”). Jurisdictions that permit the introduction of package inserts to establish the standard of care are also concerned with their potential to mislead juries about the propriety of off-label uses, but this concern is addressed not by prohibiting their use as evidence but by requiring the simultaneous production of an expert to establish that the inserts do in fact reflect the standard of care. See, e.g., *Richardson*, 44 S.W.3d at 15–17.

<sup>76</sup> *Arnold*, 2006 WL 1410161, at \*3.

<sup>77</sup> It is unclear which approach reflects the majority view. Jurisdictions in both camps purport to do so. Compare *id.* (“[W]e find that a slight majority do not allow the insert for the truth of the matters asserted within.”), with *Richardson*, 44 S.W.3d at 15 (“Virtually every court addressing this question has concluded that the drug's labeling and PDR reference are relevant to the standard of care issue.”).

<sup>78</sup> See, e.g., *Blazoski v. Cook*, 787 A.2d 910, 918 (N.J. Super. Ct. App. Div. 2002) (“The majority view . . . represented by the recent decision of the Pennsylvania Supreme Court . . . is that the doctrine of informed consent does not require surgeons to advise patients of the FDA investigational status of pedicle screws.”); Johns, *supra* note 9, at 1013 (“[R]esearch has disclosed no case holding that the doctrine of informed consent requires a doctor to disclose that a prescription is off label.”).



the patient's decision, *i.e.*, all risks potentially affecting the decision must be divulged."<sup>79</sup>

The view that off-label status is not material to a patient's decision to accept a particular course of treatment is rationalized on the wobbly ground that off-label status is a regulatory fact, not a medical fact, and thus that it does "not speak directly to the medical issues surrounding a particular [use]."<sup>80</sup> As one court recently emphasized in this regard, "the FDA does not regulate the practice of medicine, and therefore 'the decision . . . is a matter of medical judgment, not of regulatory approval.' . . . Actions for informed consent are limited to the nondisclosure of [material] medical information."<sup>81</sup> The device in question in that case was a pedicle screw used off-label as an "internal fixation device" in the context of spinal fusion surgery.<sup>82</sup> The fact that the FDA had "classified pedicle screw systems as Class III devices, 'experimental devices of unproven safety and efficacy'"<sup>83</sup> and that the agency had approved a study of pedicle screws that was ongoing at the time of the plaintiff's surgery and that required subjects to sign an informed consent form "that described the use of these screws as experimental"<sup>84</sup> did not affect the court's materiality finding. Indeed, with respect to the relevance of the ongoing study, the court explained that "[f]ederal regulations requiring that a patient be informed that the medical device is investigational apply only to investigational studies. Plaintiff was not enrolled in an investigational protocol when the surgery was performed."<sup>85</sup>

In other words, although the same experimental OLU was involved, its nature as an experiment was material and thus subject to informed consent requirements in the study setting but not in the clinical setting. The court did not attempt to rationalize this differential treatment, but it is likely based on the view that permeates this area of the law generally: that the physician-patient relationship (unlike the researcher-subject relationship) is itself sufficient protection against the harms that are the focus of the informed consent pro-

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79 *Blazoski*, 787 A.2d at 917.

80 *Id.* at 919 (quoting *Southard v. Temple Univ. Hosp.*, 781 A.2d 101, 107 (Pa. 2001)). Of course, this rationale avoids the inconvenient truths that approved, *i.e.*, "on-label," uses are such precisely and only because they have been determined to be safe and effective, and that safety and efficacy are central to medical decisionmaking.

81 *Id.* (first alteration in original) (quoting *Klein v. Biscup*, 673 N.E.2d 225, 231 (Ohio Ct. App. 1996)).

82 *Id.* at 913.

83 *Id.* at 914.

84 *Id.*

85 *Id.* at 921 (citing *Southard*, 781 A.2d at 107-08).

cess. Notably, the view that off-label status is immaterial to patients' ability to make informed decisions about their care holds even in jurisdictions that are particularly protective of decisional autonomy, where materiality is a question of fact that is to be established from the perspective of the ordinary prudent patient, not from the perspective of the relevantly educated medical provider.<sup>86</sup>

Although we have not attempted to study the matter empirically, we assume that most patients erroneously believe that the drugs their doctors prescribe for them have been determined—somehow, by someone—to be safe and effective for the uses to which they will be put in their case, and thus that they would generally consider drugs' regulatory status to be material to their decisionmaking because this status is the most commonly understood proxy for safety and efficacy.<sup>87</sup> In other words, although most patients would not necessarily use the relevant terms of art, we assume that they understand the role of the FDA to be to determine that drugs are safe and effective for the uses to which they will in fact be put, either before they are marketed to the public or postmarketing based on additional information developed in that context. We also assume that most patients erroneously believe that some regulatory scheme, for example, the law or medical ethics, prohibits physicians from experimenting with them, even ostensibly for their own good, without their express permission. Finally, we hypothesize that these patient views are especially likely to be held in this period, in which patients are less likely than in the past to have close relationships of trust with the particular medical providers who treat them, and in which medical research and the informed consent process are increasingly lay topics. If we are correct in these assumptions, it means that the law has made an unusual normative (rather than factual) judgment about the materiality of regulatory status in this context; this normative judgment is entirely in physicians' favor.<sup>88</sup>

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86 See, e.g., *id.* at 917 (noting that “[t]he doctor’s duty of disclosure is measured by the ‘prudent patient’” and not the “physician’s judgment”).

87 We base our view in part on intuition and anecdotal experience, and in part on supportive reports. See *supra* notes 9–10 and accompanying text (describing these reports).

88 The *Blazoski* case provides some additional evidence that its materiality finding was normative rather than fact based. Specifically, the court also rationalized its decision on “sound policy reasons” including that “[r]equiring disclosure may necessitate a pre-surgery discourse by the physician on the mechanics of the FDA approval process which may dilute the significance of material, medical risks related to the procedure.” *Blazoski*, 787 A.2d at 920. In this context, the court quoted the following language from a related law review article:

\* \* \* \*

In sum, state law affords physicians the liberty to engage in OLU, including problematic OLU, without relevant constraints. Specifically, neither state licensing requirements nor medical malpractice law restricts physicians' OLU other than to require that they meet the medical standard of care. However, to meet this standard in most states, it is not necessary to show that the OLU is safe or effective; it is not even required that physicians tell their patients about the dearth of medical evidence supporting their treatment choice.

### C. *The Medical Profession*

Because the federal government generally delegates the regulation of medical practice to the states, and the states generally delegate it to the profession, it is to the profession that we next turn for restriction or constraints on physicians' OLU. There are two bodies with relevant jurisdiction: state medical licensing boards and professional organizations. However, neither of these organizations provides particularly useful protections. As described above, medical licensing boards are not set up to micromanage medical practice, even though they are authorized to react to substantive evidence of gross departures from standards of care, which could include some egregious prescribing practices.<sup>89</sup>

In 1847, the AMA issued what was arguably the first code of ethics governing medical practice (the "AMA Code").<sup>90</sup> This effort was intimately entwined with the group's continuing struggle to enhance and improve the quality of medical education and the stature of doctors. The AMA remains the dominant professional group purporting to

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Patients . . . 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.

*Id.* (alteration in original) (quoting Beck & Azari, *supra* note 11, at 101).

89 For example, Dr. J. Jemsek was sanctioned by the North Carolina Medical Board for continually misdiagnosing patients as having chronic Lyme Disease and prescribing long-term intravenous antibiotics. See *Board Orders/Consent Orders/Other Board Actions: July–August 2006*, N.C. MED. BOARD, 2–3 (2006), [http://www.ncmedboard.org/images/uploads/disciplinary\\_reports/ba57.pdf](http://www.ncmedboard.org/images/uploads/disciplinary_reports/ba57.pdf).

90 See AM. MED. ASS'N, CODE OF MEDICAL ETHICS OF THE AMERICAN MEDICAL ASSOCIATION (1847), available at <http://www.ama-assn.org/ama1/pub/upload/mm/369/1847code.pdf>.

represent physicians in the United States; however, it by no means represents the majority,<sup>91</sup> and the organization itself is quick to point out that (only) its members must adhere to the principles set out in the Code.<sup>92</sup> That being said, the Code is more broadly influential; most, if not all state medical societies (often affiliates of the AMA), other medical professional organizations, and state licensing boards adhere to many of its tenets.

The relevant Principles of Medical Ethics of the AMA Code provide very generally that “[a] physician shall be dedicated to providing competent medical care, with compassion and respect for human dignity and rights,”<sup>93</sup> and that “[a] physician shall continue to study, apply, and advance scientific knowledge, maintain a commitment to medical education, make relevant information available to patients, colleagues, and the public, obtain consultation, and use the talents of other health professionals when indicated.”<sup>94</sup> An AMA policy statement that is specific to the matter of off-label prescribing “confirms” both the organization’s “strong support for the autonomous clinical decision-making authority of a physician and that a physician may lawfully use an FDA approved drug product . . . for an unlabeled indication when such use is based upon sound scientific evidence and sound medical opinion.”<sup>95</sup> With respect to a physician’s ethical obligation to prescribe drugs off-label only when such use is “based upon sound scientific evidence and . . . medical opinion,” the same statement “encourages” but does not require physicians to use “three [particular] compendia . . . and the peer-reviewed literature for determining the medical acceptability of unlabeled uses.”<sup>96</sup> Thus, the AMA frowns

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91 The AMA currently counts 236,153 members: this is fewer than thirty percent of the listed physicians in the United States. Indeed, this may be a gross overestimate. This number was current as of 2009 when it was obtained from the AMA. However, it also includes students and retired doctors, so it is unclear the exact percentage of *practicing* physicians who are members of the AMA. That the AMA membership represents a small minority of active doctors remains a valid point. See COUNCIL ON LONG RANGE PLANNING & DEV., AM. MED. ASS’N, REPORT NO. 3-A-09, DEMOGRAPHIC CHARACTERISTICS OF THE HOUSE OF DELEGATES AND AMA LEADERSHIP (2009), available at <http://www.ama-assn.org/ama1/pub/upload/mm/41/clrdp-report-3-a09-demographic.pdf>.

92 See *DoctorFinder*, AM. MED. ASS’N, <https://webapps.ama-assn.org/doctorfinder/home.jsp> (last visited Feb. 12, 2011).

93 *Principles of Medical Ethics*, AM. MED. ASS’N (rev. ed. 2001), <http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/principles-medical-ethics.shtml>.

94 *Id.*

95 *H-120.988 Patient Access to Treatments Prescribed by Their Physicians*, *supra* note 65.

96 *Id.* The compendia referred to in the policy are the AMA’s own Drug Evaluations, the United States Pharmacopeia-Drug Information, Volume I, and the Ameri-

upon, but does not prohibit, the off-label use of drugs in the absence of a significant degree of scientific evidence supporting the proposed use.

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In summary, neither the federal government nor the states via their medical licensing authority or malpractice laws has demonstrated a desire or willingness to restrain physicians from relatively unrestricted off-label use of prescription drugs. Furthermore, the medical profession itself, while professing an interest in limiting OLU to applications with a firm base in scientific evidence, has failed to exert any substantive power to implement effective regulation.

## II. THE CASE FOR LEGAL REGULATION OF PHYSICIANS' OLU

In this Part of the Article, we make the case that that physicians' OLU ought to be regulated both to protect patients' legitimate interests in evidence-based medicine and decisional autonomy and to reduce health care costs associated with problematic OLU. Specifically, we argue that the physician-patient relationship is a particularly effective point of regulation and that traditional rationales supporting unfettered physicians' liberty in this context are anachronistic and insufficient in any event to outweigh the need for effective constraints.

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can Hospital Formulary Service-Drug Information. It notes that the first two compendia "currently are being merged as the result of an alliance between the American Medical Association and the United States Pharmacopeia." *Id.* Although the policy statement purports to derive the AMA's commitment to physicians' reliance on "sound scientific evidence and sound medical opinion" from the law, it is in fact only an ethical requirement. *Id.* To the extent the law is implicated in this aspect of the policy statement, it is only in the permission it indirectly gives doctors to "use an FDA-approved drug product . . . for an unlabeled indication." *Id.* These compendia, while seemingly reliable and unimpeachable sources of unvarnished and trustworthy information about drugs and their uses that are supported by high-quality information, are actually extensively open to exploitation and undue influence by the drug companies. See ROSS MCKINNEY ET AL., WHITE PAPER: POTENTIAL CONFLICT OF INTEREST IN THE PRODUCTION OF DRUG COMPENDIA 6-7, 55-58 (2009), available at <http://www.cms.gov/determinationprocess/downloads/id64TA.pdf>; Abernethy et al., *supra* note 14, at 336. The reliability of compendia for accurate and unbiased information may be improved by a provision included in the Medicare Improvements for Patients and Providers Act of 2008, Pub. L. No. 110-275, § 182(b), 122 Stat. 2494, 2583 (amending 42 U.S.C. § 1395x(t)(2)(B) (2006 & Supp. IV 2010)), which explicitly requires these databases to openly declare any conflicts of interest and publicize their methods. See Katherine Tillman et al., *Compendia and Anticancer Therapy Under Medicare*, 150 ANNALS INTERNAL MED. 348, 349 (2009). However, the open declaration of potential conflicts of interest is not always a reliable deterrent to avoiding them.

A. *An Effective Point of Regulation*

Presumably to avoid regulation of the physician-patient relationship and because of the FDA's restricted jurisdiction otherwise,<sup>97</sup> efforts to address problematic OLU have largely focused upstream, on restricting pharmaceutical companies' promotions practices.<sup>98</sup> The notion underlying these restrictions is that if the flow of information about OLU from pharmaceutical companies to physicians can be slowed, physicians' traditional discretion will remain at least formally unaltered, but at the same time, they are likely to engage in better prescribing practices. That is, because the universe of information physicians receive about OLU is designed not to include biased information from pharmaceutical companies, prescriptions are more likely to be safe and effective.

We have already demonstrated that this strategy has largely failed to achieve its objective—biased information about OLU continues to flow relatively unabated from the companies to physicians, and problematic OLU continue to be prescribed at significant rates.<sup>99</sup> Although we support continued efforts to shore up the restrictions on pharmaceuticals' promotions practices, we also support direct regulation of physicians' prescribing practices. Regulation at the point of the physician-patient relationship is likely to be effective in ways that indirect regulation upstream, at the point of the relationship between pharmaceutical companies and physicians, has not been.

First, this is because the incentives for physicians are different. That is, unlike pharmaceutical companies, physicians' bottom line in general is not based on or even affected by sales of OLU. (We have already noted the irony that evading restrictions on the promotion of problematic OLU is good business for pharmaceutical companies, which factor penalties into the cost of doing business and still reap positive financial benefits.<sup>100</sup>) Rather, physicians' bottom line is generally based on reputation and a successful medical practice. Indeed, for the vast majority of physicians who are not involved in promoting OLU on behalf of their manufacturers, it is largely irrelevant whether a drug or biologic is an OLU or not; what matters is that it helps their patients. This means that if sanctions for violating restrictions on problematic OLU affect reputation and the opportunity for a successful medical practice, they are likely to be effective. They will deter

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97 See *supra* notes 43–45 and accompanying text.

98 See *supra* notes 6, 34–37 and accompanying text (describing this focus).

99 See *supra* notes 6–8, 34–37 and accompanying text (discussing this failure).

100 See *supra* notes 34–37 and accompanying text (noting this point).

unwarranted prescribing practices because most physicians would have little or no reason even to try to absorb related losses.

Second, regulation of problematic OLU at the point of the physician-patient relationship is likely to be effective because it would manage the transmission that ultimately matters most: the transmission of the medication to the patient who could be harmed by its use. To the extent that this transmission can be managed successfully—either restricted or qualified, depending on the state of the evidence supporting its use—it will have a net positive effect on patient welfare. This is more than a “last clear chance” argument, although it is that too. Earlier transmissions are only of information, which affects patient welfare in the long run, but only indirectly. Most important, even successful regulation upstream can never on its own effect the changes sought, since physicians can and do engage in problematic OLU even in the absence of manufacturers’ promotional efforts. Thus, unless physicians’ prescribing practices are regulated, there will always be problematic OLU and the risks of harm to patient welfare they implicate.

### B. *The Case Against Traditional Physician Liberty*

As far as we can tell, no one has yet lodged a serious argument in favor of legal regulation of physicians’ OLU-prescribing practices.<sup>101</sup> Even passing references to such regulation, however, have been forcefully rejected on the ground that we are all better off when physicians have unfettered liberty to practice medicine.<sup>102</sup> Specifically, it is argued that because medicine remains an inexact or quasiscience—part art and part science, some say<sup>103</sup>—it is essential for the protection of patients’ best interests that the law affords physicians discretion to make routine judgment calls. Relatedly, the sanctity of the physician-patient relationship is also said to provide the basis for this discretion, both on the ground that it is only within that relationship that the requisite medical and personal information necessary for good decisionmaking is known, and on the ground that respect for patients’ decisional autonomy requires that physicians be able to do what their

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101 See *supra* notes 40–42 and accompanying text (providing additional background).

102 See, e.g., Am. Soc’y of Clinical Oncology, *Reimbursement for Cancer Treatment: Coverage of Off-Label Drug Indications*, 24 J. CLINICAL ONCOLOGY 3206, 3206–07 (2006) (supporting a requirement that “Medicare contractors . . . take into account peer-reviewed literature” in order to expand coverage for off-label uses); *Asco Supports Government Report: “Off-Label Drugs: Reimbursement Policies Constrain Physicians in Choice of Cancer Therapies”*, 5 ONCOLOGY Oct. 1991, at 29, 29–30, 33.

103 See, e.g., Christopher, *supra* note 5, at 247.

patients want them to do. In other words, this argument conceives of physicians' liberty as the vehicle that safeguards both patients' physical well-being and their right to make unfettered decisions in their own interests.<sup>104</sup> Concerns that physicians may abuse their liberty to the detriment of their patients are countered by assurances that physicians' training and ethical codes together provide ample protection. More protection for patients, especially if it were to come from law, is rejected as an affront to the dignity of the profession and its fealty especially to those codes.<sup>105</sup>

Much of this is obviously right. Medicine is not an exact science. The practice of medicine is in large part defined by the inevitability and ubiquity of judgment calls, what Kathryn Montgomery calls the "radical uncertainty" of medicine.<sup>106</sup> Any regulation of the practice of medicine, whether it be by the profession itself, by law, or by some other societal institution, must recognize these realities. Assuming that patients' best interests are the shared objective, this means that discretion to make intelligent judgment calls must be afforded. It is essential to protect the physician-patient relationship, again assuming patients' best interests are the shared objective. The reasons for this include, among other things, that patient welfare (medical and otherwise) is usually going to be maximized in circumstances of trust and commitment, both of which are unlikely to exist if this one-on-one relationship either does not exist or is breached in relevant respects. Finally, the medical profession is populated by physicians whose ethical commitment and life's work is not merely to "do no harm"; it is, if at all possible, to make their patients well. The medical profession is arguably unique in these respects. But even if it is not, it is at least beyond question that respect for these commitments demands meticulous consideration of efforts, perhaps especially by outsiders, to judge physicians' judgment calls post hoc and to restrict the range of possible calls ex ante.

What is incorrect is that physicians need to be *unfettered* in their prescribing practices to achieve maximal patient welfare. Indeed, such a right as applied to problematic OLU, particularly those for which there is little to no good evidence of safety or efficacy, is antithetical to patient welfare and represents anachronistic medical eth-

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104 See *supra* notes 40–42 (describing this argument).

105 See Council on Ethical & Judicial Affairs, *Fundamental Elements of the Patient-Physician Relationship*, AM. MED. ASS'N (1990), <http://www.ama-assn.org/ama1/pub/upload/mm/code-medical-ethics/1001a.pdf>; Council on Ethical & Judicial Affairs, *The Patient-Physician Relationship*, AM. MED. ASS'N (2001), <http://www.ama-assn.org/ama1/pub/upload/mm/code-medical-ethics/10015a.pdf>.

106 KATHRYN MONTGOMERY, *HOW DOCTORS THINK* 53 (2006).



ics. It is antithetical to patient welfare to prescribe such products because they may be affirmatively harmful. Even if they are not, they preclude alternative approaches with a proven track record of effectiveness. Prescribing problematic OLU is anachronistic medical ethics because modern ethics call for evidence-based medical practice and, correspondingly, preclude experimentation outside of formalized trials with built-in safeguards to protect patient-subject health and decisional autonomy. By definition, problematic OLU are the opposite of evidence-based medical practice. And by definition, they are experimental, albeit with more or less of a basis for trusting in the outcome of the experiment depending on the degree of evidentiary support at issue. On the latter point, it has been well over fifty years since Nuremberg, when societies around the world—including the United States—rejected the notion that experimenting with patients, even ostensibly in their own interests, was permissible in the absence of consent *for the experiment*.<sup>107</sup> Where the medical profession itself has rejected as an insufficient bulwark against the harms that might come to patients in these circumstances physicians' sincere intent to "do no harm"—good faith alone is no longer the medical standard—it behooves the law to follow suit.

Arguments in favor of a laissez-faire approach to regulating OLU based on an imagined threat to either the doctor-patient relationship or the ability of physicians to practice medicine as they see fit ring hollow and are unjustified. The doctor-patient relationship has withstood such "assaults" before<sup>108</sup> and continues to tolerate such regulatory intrusion as state licensing requirements and hospital credentialing mandates for doctors. The sanctity of the physician-patient relationship is important, but it ought not to be mistaken for the ultimate objective, which is respect for physician autonomy in the best interests of the patient. Where unfettered autonomy risks harming those interests, relevant, carefully tailored restrictions should be considered. It is this work that we take up in Part III below.

### III. WHAT LEGAL REGULATION OF PHYSICIANS' OLU MIGHT LOOK LIKE

As we noted in the Introduction to this Article, it is generally agreed both that OLU unjustified by sufficient evidence of safety and

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107 See *supra* note 22 and accompanying text (describing this point).

108 For instance, the AMA notoriously lodged vociferous objections to the creation of Medicare, in part arguing that it heralded the death knell of the doctor-patient relationship and its companion, physician autonomy. See PAUL STARR, *THE SOCIAL TRANSFORMATION OF AMERICAN MEDICINE* 368 (1982).

efficacy are problematic, and that effective regulation is necessary.<sup>109</sup> In Part II, we argued that legal regulation of physicians' problematic OLU is a necessary component of effective regulation. This final Part imagines what legal regulation of physicians' OLU might look like. Our objective is not to prescribe a particular regulatory regime. Rather, it is to provide a template for what we hope will be a broader discussion of the specifics. To this end, we first set out the necessary elements of a sound regulatory scheme and follow with an analysis of possible institutional approaches.

#### A. *The Necessary Elements of a Sound Regulatory Scheme*

Based on the reasons for regulating physicians' problematic OLU—protecting patients' interests in safe and effective medication and in decisional autonomy, and protecting society from unwarranted medical costs—a sound regulatory scheme should include at least the following four elements:

##### 1. Restrictions Corresponding to Evidentiary Support

Restrictions on prescribing behavior should be based on a sliding scale that corresponds to the evidentiary support for the particular OLU. Thus, there should be no restrictions on OLU that are not problematic because they are justified by high-quality evidence. While these OLU have not gone through the formal FDA approval process, the evidence in their favor has accumulated over time and in relation to the relevant subpopulations is deemed to be the functional equivalent. In contrast, there should be an outright ban on unjustified or merely whimsical OLU. It is difficult to imagine a rational basis for extending prescribing authority in these circumstances. Indeed, we assume that unjustified OLU would be characterized as medical abuse even if they were based in an affirmative request from a patient to subject himself or herself to an unnecessary experiment. The majority of OLU in between—OLU justified by some but not high-quality evidence and OLU justified by the need or desire to innovate—should be relevantly restricted. There is room for debate about the nature and extent of such restrictions. But they might, for example, include permission to prescribe in these categories, but only in circumstances where there are no safe and effective alternatives, and only if the patient is provided with information about the state of the evidence during the consent process and the use is cataloged and

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<sup>109</sup> See *supra* notes 14–17, 33–39 and accompanying text (describing evidentiary standards and regulations on pharmaceutical marketing).

reported. Or, the former requirement—no safe and effective alternatives—might be waived for OLU justified by some but not high-quality evidence, but retained in the case of OLU justified by the need or desire to innovate.<sup>110</sup>

## 2. FDA Status as Medically Material Information in the Informed Consent Process

Physicians prescribing problematic OLU should be required to describe the state of the evidence in support of the use to the patient as part of the informed consent process. We agree in this respect with prior commentators who have argued on behalf of this requirement.<sup>111</sup> Just as their counterparts in formalized trials, patients in the OLU setting have the right to know that proposed treatment is in some respects experimental. Specifically, correcting the misimpression most patients likely have that the drugs and biologics they are prescribed are approved by the FDA for the use to which they will be put is essential to respecting their bodily integrity and decisional autonomy.<sup>112</sup>

We reject the contrary view, most prominently espoused by Beck and Azari, that providing this information would inevitably be too complicated or cumbersome for physicians, and would confuse patients unnecessarily, even to the point that they would act contrary to their own best interests.<sup>113</sup> Their 1998 article on the subject, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, has been quite influential, particularly in its central claim that a drug's FDA status is not medically material information and thus (according to standard informed consent doctrine) need not be disclosed to patients.<sup>114</sup> This claim—"it is not possible to draw any conclusion about the safety or effectiveness of a particular use of a drug . . . from the administrative/legal status of that use as off-label"<sup>115</sup>—is disingen-

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110 Importantly, others who have discussed this problem and come to similar conclusions have suggested nonbinding directives for physicians to attempt to control the most egregious practices of OLU. However, while we are extending this analysis by calling for new statutory regulation of problematic OLU as a mechanism for managing physicians' abuses of the current system, the content of these proposed regulations would be similar, if not identical to what others have recommended for nonbinding practice guidelines. See, e.g., Dresser & Frader, *supra* note 5, 476–77.

111 See, e.g., Johns, *supra* note 9, at 1023–24.

112 See *supra* notes 10–11 and accompanying text (discussing this misimpression).

113 See Beck & Azari, *supra* note 11, at 72.

114 See *id.*; see also *supra* notes 73–80 and accompanying text (describing the related case law).

115 Beck & Azari, *supra* note 11, at 84.

uous as applied to OLU that are not supported by high-quality evidence of safety and efficacy. That is, OLU in these categories are, *by definition*,<sup>116</sup> questionable in these precise respects,<sup>117</sup> and thus, FDA status is actually a perfect “proxy” for safety and efficacy.<sup>118</sup> This is particularly true since it appears that most patients mistakenly believe that FDA approval codes for safety and efficacy; in other words, *to patients*, FDA status is medically material information.<sup>119</sup>

Given these facts, it is paternalistic and antithetical to patients' decisional autonomy to hold (as Beck and Azari urge) that the FDA status of a product should, as a policy matter, be considered legally immaterial in circumstances where it would in fact be material. Long rejected is the historical view that, without their patients' knowledge or agreement, physicians should be able to decide for them what is in their best interests.<sup>120</sup> Also rejected is the notion that physicians are

116 See *supra* notes 2–5 (explaining that on-label means that the FDA put a drug through rigorous testing for safety and efficacy and off-label means it did not).

117 See *supra* notes 14–15 and accompanying text (discussing the different levels of evidentiary support for OLU).

118 See *supra* note 20 and accompanying text (setting out Beck and Azari's argument that FDA status is not a “proxy” for safety and efficacy).

119 See *supra* notes 9–11 and accompanying text (discussing this point). This is all so plain that the only way to explain Beck and Azari's argument to the contrary is that, rather than being objective scholarly commentators, they are (appropriately) vigorous advocates for their clients' (manufacturers') very particular and different concerns. To their credit, Beck and Azari disclose this affiliation at note \*\* of their article. See Beck & Azari, *supra* note 11, at 71 n.\*\*. Notably, they also acknowledge that safety and efficacy are medically material information, as is the fact that a prescription would be for an innovative use. See *id.* at 72.

120 See *Mohr v. Williams*, 104 N.W. 12, 14 (Minn. 1905) (“Under a free government, at least, the free citizen's first and greatest right, which underlies all others—the right to the inviolability of his person; in other words, the right to himself—is the subject of universal acquiescence, and this right necessarily forbids a physician or surgeon, however skillful or eminent, who has been asked to examine, diagnose, advise, and prescribe . . . to violate, without permission, the bodily integrity of his patient . . . without his consent or knowledge.” (quoting *Pratt v. Davis*, 118 Ill. App. 161, 166 (1905))), *overruled by* *Genzel v. Halvorson*, 80 N.W.2d 854 (Minn. 1957); *id.* at 14–15 (“The patient must be the final arbiter as to whether he will take his chances with [the proposed treatment], or take his chances of living without it. Such is the natural right of the individual, which the law recognizes as a legal one.” (quoting 1 EDGAR B. KINKEAD, COMMENTARIES ON THE LAW OF TORTS § 375 (1901))); *Schloendorff v. Soc'y of N.Y. Hosp.*, 105 N.E. 92, 93 (N.Y. 1914) (“Every human being of adult years and sound mind has a right to determine what shall be done with his own body.”), *abrogated by* *Bing v. Thunig*, 143 N.E.2d 3 (N.Y. 1957). Few would argue that one of the singularly significant outcomes of the Nuremberg Trials and the subsequent *Belmont Report* was to emphasize the exceptional, if not unique, importance of informed consent to the practice of medicine and clinical research. See THE BELMONT REPORT, *supra* note 38. In their influential history of informed consent, Faden and

justified in acting unilaterally to save *competent* patients from their own bad decisions. Commitment to patients' individual right of decisional autonomy means that patients decide, not their doctors, what their best interests require. Even if that decision is an unwise one from a medical or objective perspective, it is to be honored.<sup>121</sup> In these circumstances, it ought to be the case *as a matter of law* that a physician may not withhold from a patient the fact that they are being prescribed a product that is supported by less than high-quality evidence of safety or efficacy; in other words, that their treatment is, in essence, an experiment in these respects. Courts that have held otherwise—for example, courts that have concluded that because prescribing OLU in general is legal, individual OLU are fine—likely do not know that OLU vary in terms of their evidentiary support.<sup>122</sup> If they do

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Beauchamp note the historical transition of doctors' behavior and attitude in requesting permission to do something to (and for) patients:

Until recently . . . the justification of practices of disclosure and consent-seeking were strictly governed by what we shall call a *beneficence model* rather than an *autonomy model* of the physician's responsibility for the patient. The "autonomy model," as we use the term, is the view that the physician's responsibilities of disclosure and consent-seeking are established primarily (perhaps exclusively) by the principle of respect for autonomy. The "beneficence model," as we use the term, depicts the physician's responsibilities of disclosure and consent-seeking as established by the principle of beneficence, in particular through the idea that the physician's *primary* obligation (surpassing obligations of respect for autonomy) is to provide *medical* benefits. The management of information is understood, on the latter model, in terms of the managements of patients ("due care") generally. That is, the physician's primary obligation is to handle information so as to maximize the patient's medical benefits. Here, the principle of beneficence is used to provide clinical-specific meanings for the benefits and harms to be balanced by the physician.

RUTH R. FADEN & TOM L. BEAUCHAMP, *A HISTORY AND THEORY OF INFORMED CONSENT* 59 (1986) (footnotes omitted) (citations omitted). As these authors point out, the progression to the autonomy-based model leaves behind a more paternalistic template for physician-patient interactions in which the pendulum of decisionmaking power still heavily favored the doctor, whose role was to look out for what was best for the patient. The latter, more recent development, allowed for a more equalized form of power sharing; indeed, it placed the responsibility for making decisions about what was in the best interests of the patient in the correct location: with the patient herself. This is the ideal, which is what we aim for both in regulation (or legislation) and practice, certainly when it comes to informed consent for research. But, we also see a similar practice in clinical medicine, especially in the rules governing consent for procedures, surgery and the like.

121 See DOBBS, *supra* note 62, at 652–53. Only in cases where the patient is incompetent can proxy decisionmaking by physicians and others take place.

122 See *supra* notes 73–82 and accompanying text (discussing this case law).

know this, it is impossible not to conclude that they act inconsistently with modern informed consent doctrine.<sup>123</sup>

Finally, we reject as specious the argument, made by Beck and Azari, among others, that requiring physicians to disclose a product's FDA status is too onerous.<sup>124</sup> As a threshold matter, physicians ought never be permitted to prescribe a product without knowing the evidentiary basis for its use, and in particular whether it is safe and effective. Knowing its FDA status is an aspect of that inquiry, and in the modern context, neither this fact nor additional facts about the evidentiary basis for a product are difficult to find.<sup>125</sup> To the consent process itself, physicians acting in purely clinical settings are already required to obtain consent from patients in circumstances where the medical facts are difficult for laypersons to comprehend. Summarizing the state of the evidence supporting an OLU, for example in the way we have done in this Article, is not more complicated and would likely suffice in the vast majority of cases. (Here, for example, we imagine a physician telling a patient that she is recommending drug *X*, that drug *X* has passed the FDA's safety and efficacy testing for a different use, not for this use, but that there is good, although not conclusive, evidence that it may be safe and/or effective for the proposed use.) Some particularly cautious or curious patients will ask for additional details. But this is also not different from current exchanges. In any case, respect for the objectives of the consent process requires compliance.

### 3. Consideration of Sanctions for Violations

The third component of a sound regulatory scheme should be the establishment of sanctions for violations, to incentivize physician compliance with restrictions on their OLU. Many, if not most, physicians may agree with the substance of the restrictions and thus comply in the absence of sanctions. However, because the restrictions would reverse over a century of laissez-faire policies and professional culture

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123 See DOBBS, *supra* note 62, at 652–53; *supra* notes 112–13 and accompanying text (setting out this doctrine).

124 See Beck & Azari, *supra* note 11, at 72.

125 Even before the advent of the Internet and the wide accessibility to electronic databases for easily available sources of information about FDA-approved uses and indications for drugs—for example, see *About DailyMed*, DAILYMED, <http://dailymed.nlm.nih.gov/about.cfm> (last visited Feb. 11, 2011), a website maintained by the National Institutes of Health—physicians were able manually to look things up in the ubiquitous PDR, available in hospitals, libraries, and most doctors' offices (often a “gift” from drug detail men). Today, one can quickly research the quality of data for a particular drug using any one of a number of different sources.

with respect to prescribing behavior, in the absence of relevant sanctions, the regulations are likely to be ignored or even rejected by some.

There is room for debate again here about the minimum penalties that would be effective to force compliance among those in this latter group. But they might include monetary penalties for first or mild offenses—for example, a one-time prescription for an OLU justified by some but not high-quality evidence where the conditions for such use were not fulfilled. And they might include license suspensions or revocations for multiple or severe violations—for example, a persistent refusal to comply with the regulatory regime or the prescription of a knowingly unjustified OLU. Establishing the restrictions as an aspect of the standard of care would also serve an incentivizing function, as violations involving more than merely dignitary losses could provide the basis for successful malpractice claims.

A complementary or alternative approach would involve expanding the system, currently in widespread use, that authorizes payment for a particular service only when that service is supported by a valid clinical indication. In other words, rather than penalizing physicians directly, by imposing fines for regulatory violations, physicians might be penalized indirectly, by nonpayment for restricted services. For instance, many insurance companies (including Medicare and Medicaid) must approve the order for certain expensive tests (such as MRI scans), and that approval is often dependent on the rationale listed by the ordering physician. For drugs, many third-party payers maintain formulary lists of medications that are and are not covered. However, this is rarely inclusive of clinical indication, leaving enormous discretion to physicians' prescribing habits. It would not be too onerous to expand this type of scrutiny to include a clinical indication; if supported by reasonable or high-quality evidence, an OLU would be covered. If not, then the patient would have to pay out of pocket.<sup>126</sup>

#### 4. A Reporting Requirement and Safety and Efficacy Database

The fourth and final component of a sound regulatory scheme should be provision for a reporting requirement and a (nationally) centralized database of OLU. As things stand today, millions of unregulated miniexperiments take place annually, without any mech-

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<sup>126</sup> An even more exacting form of regulation would be to restrict the dispensing of drugs to those for which a valid indication exists, even for those patients who are willing and able to pay for them. However, such a move might require amending the FDA's OLU regulations accordingly.

anism for compiling and sharing the data that result. That is, unless physicians share their OLU experiences publicly by giving talks or writing papers, or patients who are harmed by OLUs themselves publicize their plight, information about safety and efficacy largely travels through the medical community via anecdote.<sup>127</sup> The goal of the reporting requirement and database would be the establishment over time of publicly accessible information about the safety and efficacy of particular OLU so that physicians and patients can in the future proceed with the maximum information possible. If OLU unsupported by high-quality evidence of safety and effectiveness are to be permitted, with or without restrictions otherwise, it is simply good public health policy to compile and make widely available the data on uses and outcomes so that, over time, the case for or against them solidifies. There are different ways this reporting requirement and database could be established and funded, including as a matter of federal law and through contributions from manufacturers interested in having their products used off-label.

### B. Possible Institutional Approaches

A critical aspect of the development of any regulatory scheme is establishing the institution or institutions that would be involved in administering restrictions and sanctions. Again in this context there are multiple possibilities. We set out several below, understanding that some are likely to be more attractive than others depending on the nature of the restrictions that are ultimately established, and given the associated costs and professional politics at issue in this context.

Notwithstanding the traditional refrain that the federal government does not regulate the practice of medicine,<sup>128</sup> its related agencies could play a role. The Food, Drug, and Cosmetics Act would likely have to be amended by Congress to provide the FDA with the

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127 This can be published or unpublished. Indeed, some authors have even lauded the importance of anecdotal "evidence" and lamented its decreasing significance. See Jeffrey K. Aronson, Editorial, *Anecdotes as Evidence*, 326 BRIT. MED. J. 1346, 1346 (2003); Jeffrey K. Aronson & Manfred Hauben, *Anecdotes that Provide Definitive Evidence*, 333 BRIT. MED. J. 1267, 1268–69 (2006); John F. Butterworth, Editorial, *Case Reports: Unstylish but Still Useful Sources of Clinical Information*, 34 REGIONAL ANESTHESIA & PAIN MED. 187, 187–88 (2009); Anne-Michelle Ruha, Editorial, *The Case Report: A Tool for the Toxicologist*, 5 J. MED. TOXICOLOGY 1, 1–2 (2009); Bill Winett, Letter to the Editor, *There Is Value in Anecdotal Reports of Relief from Migraine with Botulinum Toxin*, 15 J. MANAGED CARE PHARMACY 78, 78 (2009).

128 See *supra* note 44 and accompanying text (explaining the basis for this refrain); *infra* note 132 and accompanying text (noting the limited contexts in which the federal government has affirmatively regulated medical practice).



requisite jurisdiction—as it stands, it is generally held that this agency only has authority to regulate manufacturers<sup>129</sup>—a process that might ultimately yield the most conceptually satisfying result, but which could be quite difficult as a practical matter.<sup>130</sup> But Heath and Human Services (HHS) jurisdiction likely could be established in the absence of congressional action.

For example, perhaps most easily, HHS's Medicare protocols could be amended to provide for unrestricted payments to physicians (and coverage for patients) for OLU supported by high-quality evidence of safety and efficacy, but then restricted to no payments for OLU with less evidentiary support. This would mirror the approach currently in place for federal funding of pharmaceuticals and procedures generally.<sup>131</sup> Further, the federal approach to existing restricted pharmaceutical products—such as narcotics—could be adopted in this area, although perhaps best under the jurisdiction of an entity other than the Drug Enforcement Agency (DEA). This would provide a form of federal ban on physicians' problematic OLU, coupled with an exception for physicians who could show that the requisite conditions had been met.<sup>132</sup> Federal requirements concerning the informed consent process and for the establishment and maintenance of a national OLU database could be included within either of these approaches. Finally, a requirement that pharmaceutical companies collaborate to fund a national OLU database could be regulated by the FDA, which already has jurisdiction to address the companies' treatment of OLU.<sup>133</sup>

The states might also assume relevant jurisdiction. Indeed, approaches that provide for an important role for the states would be

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129 See *supra* notes 42–44 and accompanying text (summarizing the FDA's jurisdiction). But see Kessler, *supra* note 7, at 698 (arguing otherwise).

130 See Christopher, *supra* note 5, at 247.

131 See, e.g., Am. Soc'y of Clinical Oncology, *Reimbursement for Cancer Treatment: Coverage of Off-Label Drug Indications*, 24 J. CLINICAL ONCOLOGY 3206, 3206–07 (2006); Joshua Cohen et al., *Off-Label Use Reimbursement*, 64 FOOD & DRUG L.J. 391, 391–403 (2009); Darren A. DeWalt et al., *Significance of Medicare and Medicaid Programs for the Practice of Medicine*, 27 HEALTH CARE FINANCING REV. 79, 79–90 (2005); Su-Ying Liang et al., Letter to the Editor, *Medicare Formulary Coverage for Top-Selling Biologics*, 27 NATURE BIOTECHNOLOGY 1082, 1082–84 (2009).

132 Physicians' prescribing practices are already federally regulated when the drugs at issue fall within the Drug Enforcement Agency's jurisdiction. See Controlled Substances Act, 21 U.S.C. §§ 801–904 (2006). Registration is required for a physician to prescribe controlled substances, and that registration is contingent on following DEA regulatory provisions. See *id.* § 823(f).

133 See *supra* notes 6, 34–36, 43–45 and accompanying text (discussing the FDA's related jurisdiction).

most consistent with the longstanding political position that the practice of medicine is the proper business of the states, and thus they might elicit less knee-jerk opposition. The key players in this context would be the legislature, the medical licensing boards, and the courts.

State legislatures could act, either pursuant to federal mandate or on their own, to codify informed consent and reporting (to the database) requirements. Restrictions on OLU prescribing practices according to the sliding scale of evidentiary justification could be similarly imposed. These requirements could be established and administered by the states and their departments of health and human services, or they could be codified as part of the states' medical licensing acts. Among other things, these acts set out the legal obligations and authority of local medical licensing boards.<sup>134</sup> To the extent that statutory deference to the boards would be preferred, for example because this approach would effect a more minor revolution and thus be less objectionable politically, it would be essential to enhance the boards' jurisdiction and authority, and especially to require their vigorous pursuit of violators.<sup>135</sup>

State courts acting in malpractice cases could play a role, not only in applying any statutory reforms that emerge from these proposals, but in the first instance in better applying existing law. Although there are only a few reported cases in this area, they generally reflect a lack of understanding of the facts of OLU, and in particular of their widely varying evidentiary justifications. Relatedly, some also reflect an anachronistic tendency both to defer to physicians' judgment regardless of its evidentiary basis, and to patronize patients as they interpret the mandates of informed consent law.<sup>136</sup>

Finally, insurance companies could be useful institutional partners in any regulatory scheme. Insurance companies operate in much the same way as Medicare to effect indirect but powerful limits on physicians' medical practice and choices. That is, if neither Medicare nor an insurance company will pay a physician for services associated with problematic OLU-prescribing practices, or pay for the drug involved, it is likely that such practices will cease or at least be substantially limited. The role that insurers and Medicare already play in limiting treatment options is controversial, as it is seen by many as an

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134 See, e.g., N.C. GEN. STAT. § 90-5.1 (2009) (empowering and requiring the board to, for example, "[d]evelop and implement methods to identify . . . physicians who fail to meet acceptable standards of care" and to "[d]evelop and implement methods to ensure the ongoing competence of" licensed physicians).

135 See *supra* Part I.B.1, .3 (discussing the current role and limitations of the states' medical licensing boards).

136 See *supra* Part I.B.2 (describing this case law).

inappropriate invasion of the physician-patient relationship and restriction on patients' (at least moral) rights to the best treatment available.<sup>137</sup> We generally agree that this critique is legitimate. However, to the extent that insurance companies' role can be managed so that it is limited to restricting or prohibiting only bad—as in potentially unsafe and/or ineffective, rather than merely expensive—medications, it ought to be considered.

### CONCLUSION

There are a few relationships that society treats as sacrosanct. These relationships are embedded within a zone of privacy that is considered (at least in theory) to be impenetrable. The physician-patient relationship is one of these, along with, *inter alia*, the parent-child relationship and the spousal relationship. The physician-patient relationship and others like it are justified as categorically different from others not so sacrosanct on the grounds that their exchanges are qualitatively more significant than those that occur in other contexts and that interference from outsiders is more likely to be harmful than helpful to the interests they are designed to protect. The law largely reflects these political and social norms. The parent-child, spousal, and physician-patient relationships, for example, are largely insulated (again, at least formally) by constitutional provisions, statutes, and case law, from state and sometimes even private actions that would affect their conduct.

Notwithstanding this exceptional social status, relationships in this category, including the physician-patient relationship, are not and should not be absolutely inviolate. Where the government has an important enough interest in intervention, breaching the zone of privacy is appropriate and thus ought to be permissible. For example, where parents, who are otherwise presumed to act in their children's best interests, risk them serious physical injury, the law authorizes state intervention in the relationship. Similarly, where physicians' prescribing practices, also ordinarily presumed to be in their patients' best interests, risk them unnecessary harm, the law ought to authorize intervention and appropriate restrictions. In both contexts, although deference to the primary decisionmaker remains strong, the reasons

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137 See, e.g., Am. Soc'y of Clinical Oncology, *supra* note 131, at 3206–07; Joëlle Y. Friedman et al., *The Medicare Modernization Act and Reimbursement for Outpatient Chemotherapy*, 110 *CANCER* 2304, 2310–12 (2007) (noting concern of commentators that Medicare patients' access to care would suffer as a result of the Medicare Modernization Act, but finding no empirical support that the Act negatively affected patients); Tillman et al., *supra* note 96, at 348–50.

for the special zone of privacy no longer support its absolute protection.

In this Article, we argue for the first time that the state ought to intervene in the otherwise sacrosanct physician-patient relationship when physicians prescribe medicine off-label that is not justified by high-quality evidence of safety and efficacy. It is a circumstance that warrants outsider protection of the vulnerable party to the relationship—the patient—because it involves more risk than is appropriate according to contemporary ethical standards of evidence-based medicine and because prescriptions in this category are essentially equivalent to an unregulated experiment. As it is given in other sacrosanct relationships, due deference should continue to be given to physicians as restrictions are developed to regulate this prescribing practice. For example, some prescriptions in this category will be appropriate and thus ought to be permitted even if they are justified only by some, although not high-quality, evidence of safety and efficacy. The deference cannot be so broad, however, as to include the right that exists today to proceed unfettered with entirely or insufficiently unjustified prescriptions in the absence of fully informed consent.

This is no small matter: Off-label uses of drugs are commonplace, accounting for approximately twenty percent of all prescriptions written in the United States, and a majority of those written by specialists in pediatrics and oncology. An important number of these lack basic evidentiary support.<sup>138</sup> Perhaps most striking is that the majority of patients and many of their physicians appear not to know that the drugs they are using have not been relevantly tested for safety and efficacy.<sup>139</sup>

These facts should be sufficient on their own to support regulations that would ensure both that physicians and patients know the evidentiary basis for the drugs they use and that the use of drugs with little to no evidentiary basis is appropriately restricted. The failure of alternative regulatory approaches—primarily regulation of pharmaceutical companies' off-label promotions practices—to address the problem of unsubstantiated off-label drug use provides an additional important rationale. Legal regulation of problem prescribing is likely to be much more successful because it goes directly to the exchange that matters most and because physicians' incentives could be altered to ensure compliance with relevant restrictions.

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138 See *supra* note 8 and accompanying text.

139 See *supra* notes 9–10 and accompanying text.

