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# Off-label drug promotion and the ephemeral line between marketing and education

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## ABSTRACT

Fueled by massive settlements and concerns about pharmaceutical company influence over medical practice, the fight over off-label promotion has become a rancorous one with little middle ground. For some, off-label restrictions are both bad law and bad medicine, violating the First Amendment while denying physicians access to crucial information. For others, the battle pits the very soul of the FDA against the excesses of a profit-driven marketplace. Far from ameliorating concerns over manufacturer influence, the New Model proposed by Bennett et al. would exacerbate them. The Model would limit FDA authority to core communications proposing immediate commercial transactions, giving manufacturers unfettered discretion over scientific exchanges and nearly free rein over truthful quasi-commercial communications. Most problematically, the New Model relies on the longstanding assumption that truly educational and scientific activities can be distinguished from simple product promotion – a dichotomy that exists not only in federal law and professional association codes, but also underlies the jurisdiction of the federal agencies overseeing the pharmaceutical sector. Experience invites skepticism that these activities can be cleanly separated, suggesting that the New Model may simply perpetuate abusive behaviors without offering concomitant benefits to physicians or patients.

## I. INTRODUCTION

Fueled by massive settlements under the Civil False Claims Act<sup>1</sup> and concerns that the influence of drug manufacturers now extends beyond marketing to affect the practice

<sup>1</sup> 31 U.S.C. § 3729 et seq. (2012 & Supp. I 2013).

of medicine itself, the fight over off-label drug promotion is a rancorous one with little middle ground. For some, the longstanding Food and Drug Administration (FDA) efforts to restrict off-label communications are both bad law and bad medicine, violating the First Amendment while denying physicians access to crucial prescribing information. For others, this is a battle for the very soul of the FDA, pitting scientific integrity against the excesses of a profit-driven marketplace.

The limited evidence to date on off-label drug use has only added to the furor. In 2006, Radley et al. reviewed a database of physician–patient encounters involving medication therapy, comparing patient diagnoses to recognized drug uses.<sup>2</sup> The authors estimated that 21 per cent (150 million) of the outpatient prescriptions reviewed had been written for off-label uses, and that 73 per cent of such uses ‘had little or no scientific support’—yet acknowledged that they might have overlooked uses with *some degree* of scientific support falling short of their threshold.<sup>3</sup> The study thus offered a glimpse into the extent of off-label prescribing, and highlighted the importance of differentiating between clinically appropriate and inappropriate indications. While some commentators interpreted the study as evidence of the appalling extent of inappropriate and dangerous off-label prescribing, however, others read it to establish that at least in some circumstances, off-label use is ‘the norm rather than the exception’.<sup>4</sup>

Into this fray comes the New Model for regulating drug promotion, proposed by Bennett et al.<sup>5</sup> Seeking to balance the need for FDA oversight with the First Amendment rights of drug manufacturers to communicate accurate and timely scientific information to physicians, the New Model would limit FDA authority to Core Communications proposing immediate commercial transactions, giving manufacturers unfettered discretion over Scientific Exchanges and nearly free rein over truthful quasi-commercial Non-Core Communications. Far from ameliorating concerns over manufacturer influence, however, the New Model might well exacerbate them—enshrining in law the very practices that have drawn the most scrutiny.

## II. CONCERN OVER INDUSTRY REACH

Drug manufacturers influence medical practice in a variety of ways: through explicitly promotional efforts such as advertising, through the sharing of scientific information, and by generating information through medical research. Off-label communications, by their very nature, cross several of these categories. To the extent the goal is (eventually) to sell products, communications seem by definition to ‘promote’ a sale. Even when communications are more ‘informational’, seeking to convey data to physicians or payers, they often are undertaken with the hope of convincing those audiences to

<sup>2</sup> David C. Radley, Stan N. Finkelstein & Randall Stafford, *Off-Label Prescribing Among Office-Based Physicians*, 166 ARCH. INT. MED. 1021 (2006).

<sup>3</sup> *Id.* at 1026. See also American Society of Clinical Oncology, *Reimbursement for Cancer Treatment: Coverage of Off-Label Drug Indications*, 24 J. CLIN. ONCOL. 3206 (2006) (estimating that half of the uses for cancer drugs are off-label).

<sup>4</sup> *Amarin Pharma, Inc. v. U.S. Food & Drug Admin.*, — F. Supp.3d —, No. 15 Civ. 3588(PAE), 2015 WL 4720039 (S.D.N.Y. Aug. 7, 2015) at 3. But see Marc A. Rodwin, *Rooting Out Institutional Corruption to Manage Off-Label Use*, 41 J. L. MED. & ETHICS 654, 655–6 (2013) (describing ‘frequent lack of scientific support’ and arguing that off-label use ‘makes clinical sense as an exception rather than as the rule’).

<sup>5</sup> Alan Bennett et al., *Back to First Principles: A New Model for the Regulation of Drug Promotion*, 2 J. L. & BIOSCI. 168 (2015).

prescribe (or pay for) the company's products.<sup>6</sup> Moreover, scientific information often is generated through studies sponsored or otherwise supported by manufacturers. In the modern age, then, drug manufacturers function as purveyors of *information* as well as of *products*, and the change may be met with skepticism.

It is impossible to separate the furor over off-label promotion from the ongoing debate regarding the extent of industry influence over medical practice. By the mid-2000s, medical ethicists had begun to criticize the extensive entanglements between the industry and the medical profession, ranging from gifts both small (free lunches) and lavish (all-expense-paid trips) to lucrative consultancy agreements, control of clinical studies, and ghost-written journal articles.<sup>7</sup> Presuming that manufacturers would be unlikely to spend billions of dollars on efforts that were not expected to bear fruit, critics chronicled the ways in which the industry had adapted social psychology research to target the most effective interventions—such as using other medical and scientific professionals as 'key opinion leaders' to influence their colleagues' prescribing behaviors.<sup>8</sup> Public skepticism of the industry has been heightened by the hundreds of pharmaceutical fraud settlements in recent years, as well as well-publicized allegations that manufacturers have withheld unfavorable study results and falsely styled marketing efforts as 'clinical research'.<sup>9</sup>

### III. THE NEW MODEL AND THE DIFFICULTY OF SEPARATING MARKETING FROM EDUCATION

The New Model acknowledges that off-label communications may simultaneously serve different purposes, yet remains anchored by a vision of drug manufacturers functioning as sources of valuable scientific information rather than merely product vendors. The authors argue that '[n]ot all manufacturer communications are intended to propose an immediate commercial transaction for a drug; indeed, many modern communications by manufacturers are more than promotional and are intended to provide healthcare professionals with the most accurate, up-to-date medical information to inform their medical decision-making'.<sup>10</sup> From this premise flows a deceptively simple proposal: while the FDA would maintain its regulatory authority over Core

<sup>6</sup> But see *Id.* at 28 ('Although all manufacturer communications may be at least in some part commercially-motivated, some communications do far more than propose a commercial transaction.'). Rodney A. Smolla, *Off-Label Drug Advertising and the First Amendment*, 50 WAKE FOR. L. REV. 81, 99 (2015) (arguing that some prescription-related information is 'not commercial in any intrinsic sense, but [is] rather data germane to ... medical practice').

<sup>7</sup> See eg HOWARD BRODY, *HOOKED: ETHICS, THE MEDICAL PROFESSION, AND THE PHARMACEUTICAL INDUSTRY* (2007); David Grande et al., *Effect of Exposure to Small Pharmaceutical Promotional Items on Treatment Preferences*, 169 ARCH. INT. MED. 887 (2009) (concluding that '[s]ubtle exposure to small pharmaceutical promotional items influences implicit attitudes toward marketed products among medical students').

<sup>8</sup> See eg Sunita Sah & Adriane Fugh-Berman, *Physicians Under the Influence: Social Psychology and Industry Marketing Strategies*, 41 J.L. MED. & ETHICS 665 (2013); Sergio Sismondo, *Key Opinion Leaders and the Corruption of Medical Knowledge: What the Sunshine Act Will and Won't Cast Light On*, 41 J. L. MED. & ETHICS 635 (2013).

<sup>9</sup> See eg Sammy Almashat & Sidney Wolfe, *Pharmaceutical Industry Criminal and Civil Penalties: An Update*, Sept. 27, 2012, <http://www.citizen.org/documents/2073.pdf> (last accessed Oct. 30, 2015) (identifying 239 drug company settlements totaling \$30.2 billion between 1991 and July 2012); Samuel D. Krumholz, David S. Egilman & Joseph S. Ross, *Study of Neurontin Titrated to Effect, Profile of Safety (STEPS) Trial*, 171 ARCH. INT. MED. 1100 (2010) (concluding that major clinical trial was actually a 'seeding' trial designed to increase prescriptions).

<sup>10</sup> Bennett et al., *supra* note 5 at 3.

Communications such as package inserts, the agency would have no authority to regulate Scientific Exchange and Other Exempt Communications, and could only regulate Non-Core Communications (including the use of medical liaisons and sponsored speaker presentations to healthcare professionals) that were ‘false and misleading’—a concept that would be assessed under a more flexible standard than the substantial evidence needed to obtain FDA approval of a new indication.<sup>11</sup>

The authors seek to style the New Model as a response to the clash between modern communications platforms and the outdated FDA regulatory regime, yet the characterization is not entirely convincing. While electronic media enable manufacturers to communicate with physicians and patients more quickly and in new ways, the core *nature* of those communications is not new. Drug manufacturers seek—both by definition and by the necessities of the for-profit corporate form—to *sell* their products. Facebook and Twitter are no guarantees that a manufacturer will enhance its altruistic scientific profile, any more than reliance on print manuscripts signaled the opposite. In short, there is little new about drug manufacturers seeking to share an ever-wider range of information with prescribers than that contained in the official labeling, other than the manner in which communications now take place.

Rather than providing an innovative response to those changes in light of recent First Amendment developments, however, the New Model relies on traditional assumptions about manufacturer motivations. One of the most striking aspects of pharmaceutical policy in the United States has been the longstanding belief that truly ‘educational and scientific’ activities can be separated from simple product promotion. The dichotomy is evident in the respective roles of the federal government agencies that oversee the pharmaceutical sector: the FDA serves as the arbiter of scientific evidence, while the Department of Health and Human Services Office of Inspector General (OIG) assures that the medical care provided to Medicare and Medicaid beneficiaries is not influenced by improper promotional practices, including financial incentives offered to prescribers.

The authors’ assumption that manufacturer activities can be neatly sorted into either the promotion or science/education category echoes a belief long reflected in federal law and guidance. Rather than flatly prohibiting industry participation in medical education, for example, the FDA has sought to distinguish activities undertaken to market products from those that support truly independent scientific and educational exchange. When the agency finalized early guidance on industry support of continuing medical education (CME) in 1997—the documents that gave rise to the initial First Amendment challenges<sup>12</sup>—the agency focused on the extent to which a ‘company is in a position to influence the presentation of information related to its products or otherwise transform an ostensibly independent program into a promotional vehicle’.<sup>13</sup> Relevant considerations included who controlled the content and selection of speakers, whether there had been full disclosure of manufacturer funding, whether unapproved uses were discussed, whether the focus was educational rather than commercial, and who selected the audience—with particular concern for the involvement of sales and

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<sup>11</sup> *Id.* at 35, 45.

<sup>12</sup> See eg *Washington Legal Foundation v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998).

<sup>13</sup> United States Food and Drug Administration (FDA), *Final Guidance on Industry-Supported Scientific and Educational Activities*, 62 Fed. Reg. 64,074, 64,095 (Dec. 3, 1997).

marketing personnel.<sup>14</sup> A similar distinction appeared in a 1996 guidance document addressing the distribution of journal reprints and reference texts containing off-label information, which the agency sought to limit to ‘reprints of articles that represent the peer-reviewed, published version of original efficacy trials’, as well as ‘sound, authoritative materials that are written, published, and disseminated independent of the commercial interest of a sponsoring company and are not false or misleading’.<sup>15</sup> Nearly 20 years later, however, these guidelines remain in flux.<sup>16</sup>

The OIG adopted a similar stance in its 2003 *Compliance Program Guidance for Pharmaceutical Manufacturers*. Manufacturers were advised to keep grantmaking separate from sales and marketing activities, establish grant criteria that did not take product purchases into account, assure that funded activities were bona fide, and exercise no control over speakers or presentation content.<sup>17</sup> OIG recommended that true research grants be insulated from sales and marketing influences, and that research-related contracts with potential prescribers be structured to fit the Anti-Kickback Statute personal services safe harbor.<sup>18</sup> Consistent with this advice, OIG warned that research activities originating through sales and marketing efforts would face particular scrutiny. Thus, the potential conflation of research and sales motivations has been a core concern shared by both agencies.

The dichotomy has also been reflected in the voluntary codes adopted by the American Medical Association (AMA) and the major pharmaceutical trade associations, particular regarding support for CME. The AMA’s *Guidelines on Gifts to Physicians from Industry*, adopted in 1990 and revised in 2001, warned that educational gifts to physicians must have independent educational value, that company-sponsored clinical investigator meetings must have a ‘genuine research purpose’, and that conference subsidies should be given to the sponsor rather than to individual attendees.<sup>19</sup> The Code of Medical Ethics warns that ‘financial or in-kind support’ from drug and device companies may ‘create[] conditions in which external interests could influence the availability and/or content of CME activities.’<sup>20</sup> Where support is necessary, the Code insists on ‘vigorous efforts ... to maintain the independence and integrity of educational activities’, including full disclosure of financial interests and ‘taking steps to mitigate potential influence...’<sup>21</sup>

The Accreditation Council for Continuing Medical Education (ACCME) *Standards to Ensure the Independence of CME Activities* similarly require CME providers to assure that program ‘decisions were made free of the control of a commercial interest’ and to

<sup>14</sup> *Id.* at 64,096, 64,099.

<sup>15</sup> FDA, *Advertising and Promotion; Guidances*, 61 Fed. Reg. 52,800, 52,801 (Oct. 8, 1996).

<sup>16</sup> The latest revised guidance was issued in 2014. See FDA, *Guidance for Industry Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices*, Feb. 2014, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM387652.pdf> (last accessed Oct. 30, 2015).

<sup>17</sup> Office of Inspector General (OIG), *Compliance Program Guidance for Pharmaceutical Manufacturers*, 68 Fed. Reg. 23,731, 23,735 (May 5, 2003).

<sup>18</sup> *Id.*; 42 C.F.R. § 1001.952(d) (2014) (safe harbor).

<sup>19</sup> Council on Ethical and Judicial Affairs (CEJA), *Gifts to Physicians from Industry*, 265 JAMA 501 (1991); CEJA, *Guidelines on Gifts to Physicians From Industry: An Update*, 47 FOOD & DRUG L. J. 445 (1992); CEJA, *Guidelines on Gifts to Physicians from Industry: An Update*, 56 FOOD & DRUG L. J. 27, 33, 35–56 (2001).

<sup>20</sup> AMERICAN MEDICAL ASSOCIATION, *AMA CODE OF MEDICAL ETHICS*, Op. 9.0115 (Nov. 2011).

<sup>21</sup> *Id.*

keep promotional activities such as advertisements separate from CME activities (eg banning corporate logos and drug trade names from educational materials).<sup>22</sup> Likewise, the Pharmaceutical Research and Manufacturers of America (PhRMA) *Code on Interactions with Healthcare Professionals*, issued in 2002 and updated in 2008, warns that '[i]nteractions should be focused on informing healthcare professionals about products, providing scientific and educational information, and supporting medical education'.<sup>23</sup> And yet, despite near unanimity about the need to distinguish between scientific and promotional activities, the rate of investigations and settlements indicates the line is anything but clear.

By exempting Scientific Exchange from FDA oversight and privileging the scientific over the commercial aspects of Non-Core Communications, Bennett et al. not only perpetuate the fiction underlying this distinction, but also suggest that the drug manufacturer's role is *primarily* scientific and educational. The FDA is misguided, they argue, in emphasizing the promotional elements of manufacturer distribution of medical reprints to physicians, an activity 'intended primarily to educate, rather than propose an immediate sale of the drug'.<sup>24</sup> At one level the criticism is correct, of course: unless the person distributing the reprint is seeking the prescription for him/herself—a situation raising conflicts too numerous to name—the conversation will not result in a sale on the spot. Indeed, even a straightforward advertisement does not result in an *immediate* drug sale; for that, the patient must obtain the prescription and take it to a pharmacy. And yet that reprint or advertisement could well affect whether the physician prescribes the drug for the next patient who walks through the door. 'Immediate sale' may be a relevant concept for First Amendment analysis, but it offers an incomplete explanation of the dynamics of prescription decision-making.

Moreover, the authors' construction of their categories is not persuasive. For example, discussions between medical science liaisons (MSLs) and healthcare professionals are characterized as Non-Core Communications because MSLs are employed to serve as scientific resources rather than sales representatives, and because they 'are communicating to an educated audience of healthcare professionals who have the expertise to evaluate the merits of the information' under discussion.<sup>25</sup> Yet the literature is replete with examples of the inordinate influence that scientific and medical experts may wield by virtue of their stature and training, particularly when housed in the sales and marketing rather than the research and development department.<sup>26</sup> Simply restating the distinction does not make it true; experience invites skepticism that these activities can be cleanly separated, raising the specter that the New Model may simply perpetuate abusive behaviors without offering concomitant benefits.

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<sup>22</sup> ACCME, *Standards for Commercial Support: Standards to Ensure Independence in CME Activities*, Standards 1.1 & 4.3 (Feb. 2012), <http://www.accme.org/requirements/accreditation-requirements-cme-providers/standards-for-commercial-support> (last accessed Oct. 30, 2015).

<sup>23</sup> PhRMA, *Code on Interactions with Healthcare Professionals* (2008) at 4, [http://www.phrma.org/sites/default/files/pdf/phrma\\_marketing\\_code\\_2008.pdf](http://www.phrma.org/sites/default/files/pdf/phrma_marketing_code_2008.pdf) (last accessed Oct. 30, 2015).

<sup>24</sup> Bennett et al., *supra* note 5, at 28. The 'immediate sale' requirement is drawn from Supreme Court jurisprudence defining commercial speech. See eg *Bolger v. Youngs Drug Products Corp.*, 463 U.S. 60, 66 (1983) (discussing factors that support commercial nature of speech).

<sup>25</sup> Bennett et al., *supra* note 5, at 41.

<sup>26</sup> See eg Sah & Fugh-Berman, *supra* note 8.

#### IV. CONCLUSION

In an ideal world, patients would trust their physicians to prescribe medications solely on the basis of the available medical evidence. Physicians would be able to trust that the scientific information they received about prescription drugs—whether presented at professional meetings, published in medical journals, or discussed during sales calls—was comprehensive, reliable, and unbiased. And drug manufacturers would strive to increase their sales, but only by selling their products for conditions truly warranting the treatment. But we do not live in an ideal world, and it has become abundantly clear that these assumptions may no longer apply (if indeed they ever did). Drug manufacturers clearly distribute information as well as products, and the reliability of both has come into question.

The New Model is grounded in an unfailing belief in the drug industry as a font of trustworthy scientific information. Yet that belief is belied by recent experience. Perhaps it once was possible to trust that drug manufacturers embodied science as ‘a priesthood, an aristocracy of excellence informed by a deep sense of moral obligation’.<sup>27</sup> But that trust has long been lost, based in no small part on instances where the industry intentionally conflated science and marketing—the very dichotomy on which the New Model relies. In short, immunizing drug manufacturers from scrutiny by enshrining into law long-unsatisfactory distinctions is neither good law nor good medicine.

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<sup>27</sup> LINDA MARSA, *PRESCRIPTION FOR PROFITS: HOW THE PHARMACEUTICAL INDUSTRY BANKROLLED THE UNHOLY MARRIAGE BETWEEN SCIENCE AND BUSINESS* 17 (1997).