

8-1-2012

## The Informational and Institutional Theories of Off-Label Promotion

Miguel A. Lopez

Follow this and additional works at: <https://digital.sandiego.edu/sdlr>

 Part of the [Consumer Protection Law Commons](#), and the [Medical Jurisprudence Commons](#)

---

### Recommended Citation

Miguel A. Lopez, *The Informational and Institutional Theories of Off-Label Promotion*, 49 SAN DIEGO L. REV. 913 (2012).  
Available at: <https://digital.sandiego.edu/sdlr/vol49/iss3/10>

This Article is brought to you for free and open access by the Law School Journals at Digital USD. It has been accepted for inclusion in *San Diego Law Review* by an authorized editor of Digital USD. For more information, please contact [digital@sandiego.edu](mailto:digital@sandiego.edu).

# The Informational and Institutional Theories of Off-Label Promotion

MIGUEL A. LOPEZ\*

## TABLE OF CONTENTS

I.	INTRODUCTION .....	914
	A. <i>The Informational Theory</i> .....	915
	B. <i>The Institutional Theory</i> .....	916
II.	THE TEXT .....	917
	A. <i>Misbranding</i> .....	918
	B. <i>New Drug</i> .....	921
III.	THE INFORMATIONAL THEORY .....	923
	A. <i>The Normative Framework</i> .....	923
	B. <i>The Customary Approach</i> .....	927
	C. <i>The EBM Movement</i> .....	931
	D. <i>Clinical Practice Guidelines</i> .....	936
IV.	THE INSTITUTIONAL THEORY .....	938
	A. <i>The Normative Framework</i> .....	938
	B. <i>Off-Label Promotion as a Conspiracy To Defraud the United States</i> .....	942
	1. <i>Statutory Background</i> .....	942
	2. <i>Klein Conspiracies</i> .....	945
	3. <i>The Regulated Benefits Formulation</i> .....	948
V.	CONCLUSION .....	953

---

\* The Author is a law clerk for Judge Ursula Ungaro of the U.S. District Court for the Southern District of Florida during the 2012–2013 term. Previously, he worked as an associate at the law firm of Ropes & Gray, LLP. Views expressed herein are solely his own. The Author received his J.D. from Harvard Law School in 2011 and his B.A. from Columbia University in 2008. He would like to dedicate this Article to his cousin Elizabeth, whose dedication to her patients and to her profession he hopes to emulate in his own career.

## I. INTRODUCTION

The government will hold pharmaceutical manufacturers liable when they market their drugs for uses not approved of by the U.S. Food and Drug Administration (FDA). The government will see to it that these corporations are held criminally liable, civilly liable, and morally blameworthy in the court of public opinion. And yet few major manufacturers have ever gone to trial following such an indictment or the filing of a criminal information. What is more, the term “off-label promotion,” commonly used by attorneys practicing in this area to describe the promotion of drug uses that are not FDA approved, is in fact absent from the relevant legislative materials. Instead, we are made aware of its existence by following an unfolding and cross-referencing chain of statutory and regulatory provisions, and by paying close attention to enforcement actions.

But where there is law, there must be answers, and making sense of government enforcement in this arena is no different. The foremost obstacle to clearly defining the law of off-label promotion has been the lack of judicial review in cases of corporate prosecution. Because criminal and civil resolution of corporate off-label charges has almost always come in the form of settlement,<sup>1</sup> there is a tendency to think of off-label promotion as being *sui generis*—guidance is neither importable nor exportable, but can only be borne of experience with this particular area of enforcement. But no area of law that so frequently witnesses multimillion-dollar settlements can possibly be so opaque.

This Article contends that there are two distinct theories of the offense of off-label promotion—the informational theory and the institutional

---

1. In the corporate criminal context, “settlement” is typically reached in one of three forms: by deferred prosecution agreements (DPAs), by consent decrees, or by corporate integrity agreements (CIAs). DPAs are the most serious form of settlement because the defendant corporation obtains repose only after a term of usually three to five years. Until then, a criminal information is filed in federal district court and may be given effect upon a material breach of the DPA’s terms. *See generally* Abigail H. Lipman, *Corporate Criminal Liability*, 46 AM. CRIM. L. REV. 359, 389 (2009) (“DPAs . . . operate like a term of probation before a conviction.”). A consent decree is an agreement between two parties, sanctioned by a court, that serves the purpose of a permanent injunction but does not adjudicate the merits of the case. *See* Local No. 93, Int’l Ass’n of Firefighters v. City of Cleveland, 478 U.S. 501, 519–24 (1986) (discussing the hybrid nature of the consent decree). CIAs work permanent changes to the defendant’s corporate structure and impose strict governance measures the breach of which carry specific penalties. CIAs are often used in conjunction with DPAs, and the fulfillment of the CIA’s terms is made a condition precedent to the satisfaction of the defendant’s DPA. *See, e.g., Corporate Integrity Agreement Between the Office of Inspector General of the Department of Health and Human Services and Pfizer Inc.*, U.S. DEP’T HEALTH & HUM. SERVICES OFF. INSPECTOR GEN. (Aug. 31, 2009), [http://oig.hhs.gov/fraud/cia/agreements/Pfizer\\_inc\\_08312009.pdf](http://oig.hhs.gov/fraud/cia/agreements/Pfizer_inc_08312009.pdf).

theory. One is concerned with controlling the flow of medical knowledge and the other is concerned with protecting regulatory legitimacy. Different kinds of evidence are key under each theory. I argue that although the Federal Food, Drug, and Cosmetic Act (FD&C Act) and its accompanying regulations emphasize the informational theory, federal prosecutors rely more heavily on the legal arguments that underpin the institutional theory of enforcement. A corollary to this contention is that the informational theory of off-label promotion does most of the work in determining the evolution of FDA policy and guidance with respect to drug marketing and labeling. The institutional theory, on the other hand, drives the blunt force of government enforcement, meant to give the regulatory system it protects an extra measure of deterrent power. I briefly summarize these two theories below.

#### A. *The Informational Theory*

The informational theory posits that off-label promotion, which is the promotion of a prescription drug for a use not approved by the FDA, is a punishable offense first and foremost because it corrupts the body of information available to physicians, thereby placing patients at risk. When emphasizing this normative justification for prosecution, Department of Justice officials focus on the sanctity of the doctor-patient relationship, and their legal arguments link off-label promotion either to the poisoning of the well from which physicians draw their up-to-date medical knowledge or to the direct undermining of physician integrity.<sup>2</sup> Apart from the criminal provisions of the FD&C Act, the informational theory informs the ancillary use of the antikickback statute<sup>3</sup> and, in the civil context, the False Claims Act.<sup>4</sup>

Under an informational theory of the offense, the government's case against a manufacturer should be assessed by reference to what is known about the ways in which physicians assimilate new information. Pharmaceutical manufacturers will turn points of knowledge diffusion into access points for effective marketing. Where off-label uses are not yet widely accepted, defendant manufacturers will target the points of diffusion. Cases built upon ambiguous evidence of interaction with the common ranks of the profession are not likely to be strong cases.

---

2. See *infra* notes 45–49 and accompanying text.

3. Anti-Kickback Act of 1986, 41 U.S.C. §§ 51–58 (2006).

4. False Claims Act, 31 U.S.C. §§ 3729–3731 (2006 & Supp. IV 2011).

The informational theory also animates some of the most contested enforcement positions taken by the FDA. Continuing Medical Education (CME) seminars and independent research publications have been intense targets of government scrutiny—especially when openly sponsored in any way by the pharmaceutical industry.<sup>5</sup> Much has been written about the First Amendment implications of government enforcement in this area,<sup>6</sup> but that dimension of the problem will not be discussed at any significant length here. This Article assumes that the grave First Amendment concerns attendant in many aspects of off-label prosecution will simply not forestall government enforcement—at least not in the near future.

### B. *The Institutional Theory*

The institutional theory posits that off-label promotion is a punishable offense first and foremost because it undermines the FDA's power to regulate the prescription drug market—again, putting patients at risk. When emphasizing this normative justification for prosecution, Department of Justice officials portray the FDA as the guardian of the public's health and wellbeing.<sup>7</sup> Off-label promotion is cast as a threat to the agency's authority because it undermines the drug approval process, thereby jeopardizing one of the agency's most fundamental missions. But it is also an offense because it frustrates the workings of government generally.

Apart from the criminal provisions of the FD&C Act, the institutional theory informs prosecutions under the federal health care fraud statute,<sup>8</sup> as well as ancillary reliance on both the offense and defraud clauses of the federal conspiracy statute.<sup>9</sup> This normative justification also rests on the conclusion that off-label promotion causes unapproved expenditures by the federal government totaling in the millions and more.<sup>10</sup> In this way, it too animates the use of the False Claims Act.

---

5. See *infra* text accompanying note 119.

6. See generally A. Elizabeth Blackwell & James M. Beck, *Drug Manufacturers' First Amendment Right To Advertise and Promote Their Products for Off-Label Use: Avoiding a Pyrrhic Victory*, 58 FOOD & DRUG L.J. 439 (2003); Margaret Gilhooley, *Drug Safety and Commercial Speech: Television Advertisements and Reprints on Off-Label Uses*, 47 SAN DIEGO L. REV. 845 (2010); Lars Noah, *The Little Agency That Could (Act with Indifference to Constitutional and Statutory Strictures)*, 93 CORNELL L. REV. 901 (2008); Edmund Polubinski III, Note, *Closing the Channels of Communication: A First Amendment Analysis of the FDA's Policy on Manufacturer Promotion of "Off-Label" Use*, 83 VA. L. REV. 991 (1997).

7. See *infra* text accompanying notes 131–33.

8. 18 U.S.C. § 1347 (2006 & Supp. IV 2011).

9. 18 U.S.C. § 371 (2006).

10. See, e.g., Jeanne Whalen et al., *Glaxo in \$3 Billion Settlement*, WALL ST. J. (July 2, 2012), <http://online.wsj.com/article/SB10001424052702304299704577502642401041730.html> (reporting that GlaxoSmithKline P.L.C. would pay \$2 billion to resolve civil liabilities owed to the federal government and the states).

When the government relies primarily on this theory of enforcement, it likely does so for one of two reasons: (1) fiscal harm to the government from false reimbursement claims outweighs perceived health risks to the affected patient population, or (2) its informational case is weak, either (a) normatively, because the off-label promotion is truthful and scientifically proven, or (b) legally, because the evidence does not comport with theories of how new medical knowledge is diffused and adopted.

Cases argued under the institutional theory for fiscal reasons should be brought solely on civil grounds unless the scheme involved other criminal elements, such as providing kickbacks for increased off-label prescribing, or instructing physicians on how to submit deceptive reimbursement claims. Cases argued under this theory—primarily because of flaws in the informational case—should be avoided as impinging too strongly on free scientific exchange. However, there is a narrow doctrinal window under the federal conspiracy statute whereby a felony charge is appropriate even under these circumstances.

## II. THE TEXT

Off-label promotion is the promotion of an approved drug for *any* purpose or use not specifically approved by the FDA, be it indication, dosage form, or patient population.<sup>11</sup> Astonishingly, it is not succinctly defined anywhere in the United States Code or the Code of Federal Regulations. Instead, one must construct the prohibition by reading a series of statutory provisions further defined—and not always intuitively so—by regulation. Actually, the government has two distinct threads of positive text along which it may arrive at the offense, and either one will suffice.<sup>12</sup> Although the more detailed route is plainly concerned with the

---

11. *Blain v. Smithkline Beecham Corp.*, 240 F.R.D. 179, 182 n.6 (E.D. Pa. 2007) (offering a broad definition of off-label promotion).

12. Courts are not always careful in distinguishing among the bases for off-label liability—at least when not directly faced with a criminal complaint. *See, e.g., In re Neurontin Mktg., Sales Practices & Prods. Liab. Litig.*, 618 F. Supp. 2d 96, 104 (D. Mass. 2009) (summarily citing 21 U.S.C. §§ 331(a), 331(d), 333(a)(2), 352(f)(1), and 355(a) as the bases for the charge of off-label marketing brought against Warner-Lambert Co. to which the company pled guilty in a related criminal action). Many commentators also fail adequately to distinguish among the statutory bases, *see, e.g.,* John E. Osborn, *Can I Tell You the Truth? A Comparative Perspective on Regulating Off-Label Scientific and Medical Information*, 10 *YALE J. HEALTH POL'Y L. & ETHICS* 299, 308–11 (2010), though others do dedicate part of their analysis to distinguishing between the two avenues of enforcement, *see, e.g.,* Allison D. Burroughs et al., *Off-*

transmission of *information*, the other is concerned with the protection of FDA authority and that agency's control over regulated industries.

### A. Misbranding

Both constructions of off-label promotion begin with 21 U.S.C. § 331, styled "Prohibited acts."<sup>13</sup> That section prohibits both "acts *and* the causing thereof."<sup>14</sup> The most oft-cited construction begins with subsection (a), which prohibits the "introduction . . . into interstate commerce of any . . . drug . . . that is adulterated or misbranded."<sup>15</sup> Although no reference is made to a definition of "misbranded" in the text, the controlling definition is found at § 352, styled "Misbranded drugs and devices."<sup>16</sup> Subsection (f) provides that a drug will be deemed misbranded "[u]nless its labeling bears . . . adequate directions for use."<sup>17</sup> This is as far as we get in the United States Code: a prohibition on the introduction of any drug whose labeling does not bear adequate instructions. For further elaboration, one must turn to the Code of Federal Regulations.

The regulations provide that "[a]dequate directions for use means directions under which the layman can use a drug safely and for the purposes for which it is intended."<sup>18</sup> But the negative definition is more useful for our purposes. Directions may be *inadequate* as a result of "omission, in whole or in part"<sup>19</sup> of "[s]tatements of all conditions, purposes, or uses for which such drug is intended, including . . . uses . . . suggested in its oral, written, printed, or graphic advertising."<sup>20</sup> Thankfully, the section directs us to a further definition of "intended use," which is defined as "the objective intent of the persons legally responsible for the labeling of drugs," which may "be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives."<sup>21</sup> Finally, the picture is clear: the law prohibits the

---

*Label Promotion: Government Theories of Prosecution and Facts That Drive Them*, 65 FOOD & DRUG L.J. 555, 558–68 (2010).

13. 21 U.S.C. § 331 (2006 & Supp. IV 2011).

14. *Id.* (emphasis added).

15. *Id.* § 331(a).

16. *Id.* § 352.

17. *Id.* § 352(f).

18. 21 C.F.R. § 201.5 (2011).

19. *Id.*

20. *Id.* § 201.5(a).

21. *Id.* § 201.128; see also Gregory Gentry, *Criminalizing Knowledge: The Perverse Implications of the Intended Use Regulations for Off-Label Promotion Prosecutions*, 64 FOOD & DRUG L.J. 441, 443 (2009) ("There is a distinction in the regulations, then, between the 'objective intent,' which determines the intended use of the product, and the subjective knowledge of the manufacturer, which could change the intended use."). It is reasonable to think of this objective intent concept as an oxymoron of sorts. See *id.*

introduction of any drug whose labeling does not provide directions for uses suggested by the manufacturer through oral or printed advertisement.

When assessing whether this prohibition has been transgressed, the inquiry should actually begin with the final step, 21 C.F.R. § 201.128, and work its way up to the statutory prohibition. To illustrate: (1) a manufacturer's promotion of an off-label use makes that use an *intended* use of the drug, such that (2) the FDA-approved directions on the label are rendered inadequate, thus (3) causing the drug to be misbranded. Stated this way, it becomes clear that the prohibition is concerned first and foremost with the perceived intended uses of a drug, and that a prime agent of that perception is drug marketing. The informational theory of enforcement thus seeks to control changes in intended use over time<sup>22</sup> by deterring certain persons—namely manufacturers and their representatives—from contributing to information about the drug beyond the materials already on the label.

There are, of course, gray areas in which reasonable minds could differ on whether the marketing at issue actually does create a gap between the intended use of a drug and the on-label instructions. This will be explored more fully in Part III. As a textual matter, it is important to note that the FD&C Act's "Definitions" section provides instructions by which the fact finder could at least assess whether the labeling or advertising is *misleading*.<sup>23</sup> Section 321(n) even instructs us on the sin of omission:

If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account . . . also the extent to which the labeling or advertising *fails to reveal facts material* [1] in light of such representations or material with respect to consequences which may result . . . under the conditions of use prescribed in the labeling or advertising thereof *or* [2] under such conditions of use as are customary or usual.<sup>24</sup>

Given that subsection (n) gives instructions for finding that certain advertising is misleading even as to approved uses, its sweep is broader than the off-label offense alone. Still, it seems to mandate that a manufacturer itself police the off-label promotion of its drug—even by others—by warning against such uses in its own labeling or advertising.

---

22. The FDA explicitly recognizes that "intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer." 21 C.F.R. § 201.128.

23. See 21 U.S.C. § 321(g)(1), (n) (2006).

24. *Id.* § 321(n) (emphasis added).

Failing to do so would constitute the “fail[ure] to reveal facts” deemed indicative of misbranding.<sup>25</sup>

In the context of off-label uses, the duty not to omit material facts could play out in a number of ways.<sup>26</sup> Suppose, for example, that Drug X is approved for Indication Y and that all its labels and print materials—which together constitute “labeling”<sup>27</sup>—reveal all material facts, and that its verbal marketing of Drug X is not to the contrary. Now suppose that Drug X is frequently prescribed for Indication Z, a slightly less severe variant of Indication Y, for which Drug X is not FDA-approved. Drug X’s manufacturer could be liable for misbranding in at least two scenarios under § 331(n). First, if the government alleges that Drug X advertising ambiguously implies that it is effective for treating Indication Z, a fact finder could determine that, even if unintentional, the ambiguous nature of the advertisement constituted a material omission of the disclaimer that Drug X is not approved for Indication Z. This renders the advertisement misleading.<sup>28</sup> Second, because Drug X is frequently prescribed for Indication Z anyway, its use in the treatment of that disease is a “customary or usual”<sup>29</sup> condition of use, and the failure to indicate that Drug X is not approved for Indication Z again renders the labeling misleading—even where there is no allegation of a suggestive claim.<sup>30</sup>

These illustrations demonstrate the breadth of the theories the government could employ on the basis of § 331(a). Although the face of that subsection alone would not necessarily lead to such expansive theories, the regulatory texts implementing the prohibition do their own work without the need

---

25. *Id.*

26. See Vicki W. Girard, *Punishing Pharmaceutical Companies for Unlawful Promotion of Approved Drugs: Why the False Claims Act Is the Wrong Rx*, 12 J. HEALTH CARE L. & POL’Y 119, 134 (2009) (noting that the vast majority of misbranding violations identified by FDA warning letters are of the omission or minimization variety).

27. See 21 U.S.C. § 321(m) (2006) (“The term ‘labeling’ means all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.”).

28. Cf. *United States v. Caputo*, 288 F. Supp. 2d 912, 921 (N.D. Ill. 2003) (discussing how promotion of off-label uses could be “potentially misleading because without the appropriate disclosures the other party may not be able to distinguish between off-label uses and FDA-approved uses”). The *Caputo* court faced a somewhat different question than posed by my hypothetical because there the promotion was assumed to be off-label, and the question was whether it was also inherently misleading. *Id.* at 920–21. However, the same rationale would apply without finding that the defendant was intentionally or specifically promoting an off-label use. See *id.* at 921.

29. 21 U.S.C. § 321(n).

30. For example, in *In re Zyprexa Prods. Liab. Litig.*, the defendant manufacturer did exercise its duty to indicate that the drug was not approved for certain frequently prescribed off-label uses. See 671 F. Supp. 2d 397, 414–16 (E.D.N.Y. 2009) (describing the part of label that read: “ZYPREXA (olanzapine) is not approved for the treatment of patients with dementia-related psychosis” (internal quotation marks omitted)).

for judicial implication. It is unlikely that a new era of judicial review of corporate off-label prosecutions would circumscribe what is rather plainly provided by the text of the FD&C Act and its accompanying regulations. From an enforcement perspective, it is possible to view the § 331(a) prohibition as being actively concerned with the policing of information and far less concerned with deterring circumvention.

### *B. New Drug*

Another way of arriving at the prohibition is through § 331(d), which addresses a complementary set of enforcement goals. This second construction of the prohibition is more straightforward and yet is concerned with a more abstract danger—challenging FDA control. Deterring regulatory circumvention is its primary goal, and the policing emphasis is at the moment of an approved indication’s birth, rather than on its subsequent development.<sup>31</sup> As with the informational danger that § 331(a) seeks to prevent, one ultimate consequence of challenging FDA control is harm to the public. But although the two constructions share at least one concern, they differ in other ways. Subsection (a) is concerned squarely with postmarket developments that it recognizes to be largely out of its control; subsection (d) is concerned with premarket processes over which the FDA has plenary power.

Only one part of § 331(d) relates to off-label promotion specifically. That subsection prohibits the “introduction . . . into interstate commerce of any article in violation of section 344, 350d, 355, or 360bbb-3 of this title.”<sup>32</sup> These sections govern, respectively, emergency permit control;<sup>33</sup> registration of food facilities;<sup>34</sup> effective approval of new drug applications;<sup>35</sup> and authorization for medical products for use in emergencies.<sup>36</sup> Only the third, § 355, is relevant to our discussion, but its inclusion among these disparate concerns suggests that this route to prohibiting off-label promotion conforms to the institutional theory of enforcement.

Section 355, styled “New drugs,” prohibits “[the] introduction into interstate commerce [of] any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is

---

31. See 21 U.S.C. § 331(d) (Supp. IV 2011); 21 U.S.C. § 355(a) (2006).

32. 21 U.S.C. § 331(d).

33. 21 U.S.C. § 344 (2006).

34. 21 U.S.C. § 350d (2006 & Supp. IV 2011).

35. 21 U.S.C. § 355 (2006).

36. *Id.* § 360bbb-3.

effective with respect to such drug.”<sup>37</sup> Turning again to the Act’s definitional section, the term *new drug* is defined as “[a]ny drug . . . not generally recognized . . . as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof.”<sup>38</sup> As alluded to above, the term *labeling* “means all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.”<sup>39</sup>

The use of the word *accompanying* in the labeling definition prong admits of the need for judicial interpretation, and fortunately that interpretation is well settled. In *Kordel v. United States*,<sup>40</sup> the Supreme Court explained: “One article . . . is accompanied by another when it supplements or explains it . . . . No physical attachment one to the other is necessary. It is the *textual* relationship that is significant.”<sup>41</sup> Implicit in this formulation is that the statutory definition of *labeling* encompasses only written materials, and that has been the accepted understanding ever since.<sup>42</sup> Whereas intended use for the purposes of § 331(a) includes statements made by any of the manufacturer’s representatives, even where they lacked actual authority to make such statements, § 355 is concerned only with material that the manufacturer must have consented to because it published the words in written material.

Section 331(d) directly relates to a failure to obtain the appropriate new drug application (NDA), and the underlying § 355 duties make the Act’s assumption evident that this breach is one condoned by the corporate entity directly. Defendants charged under this provision are most likely being accused of shooting low in their initial application, so as to get around the enormous financial and time investment needed to approve a drug for even one broad indication, let alone multiple uses.<sup>43</sup>

---

37. *Id.* § 355(a). Subsection (b) deals with the contents of an application and the filing thereof. *Id.* § 355(b). Subsection (j) deals with abbreviated new drug applications. *Id.* § 355(j).

38. *Id.* § 321(p)(1).

39. *Id.* § 321(m).

40. *Kordel v. United States*, 335 U.S. 345 (1948).

41. *Id.* at 350 (emphasis added).

42. Burroughs et al., *supra* note 12, at 559 n.22 (collecting cases).

43. See James O’Reilly & Amy Dalal, *Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, 12 ANNALS HEALTH L. 295, 304 (2003) (“Permitting off-label advertising for a drug allows the drug manufacturer to postpone committing to the approval process and thus keep research and development costs down, while still gaining the revenues from off-label sales.” (citing 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, 194 (1999))); Mitchell Oates, Note, *Facilitating Informed Medical Treatment Through Production and Disclosure of Research into Off-Label Uses of Pharmaceuticals*, 80 N.Y.U. L. REV. 1272, 1278–79 (2005) (claiming that a pharmaceutical company will, on average, spend \$880 million and

That is the cornerstone of the institutional theory of the offense, and it brings with it its own auxiliary charges and calls for the marshalling of evidence particular to that understanding of the offense.

### III. THE INFORMATIONAL THEORY

#### A. *The Normative Framework*

The harm that the misbranding provisions of the FD&C Act seek to prevent—informational corruption resulting in unproven drug treatments—should be assessed according to the ways in which drug information is diffused throughout a given field in the medical profession. That is, the alleged “access points” of marketing should line up with known “diffusion points” of new medical knowledge. Today, there are three main approaches to the acquisition of medical knowledge and its use in making treatment choices: the customary approach, evidence-based medicine (EBM), and use of clinical practice guidelines (CPGs). Because the diffusion of information varies with each of these three approaches, the ways in which a pharmaceutical manufacturer might most effectively promote its drugs for off-label uses also vary. Government claims are strongest where the alleged conduct and the dominant approach in a given field or region are aligned. Conversely, the prosecution’s case is weakest where there is a mismatch between the type of off-label promotion at issue and the specialty’s dominant method of processing and adopting new medical information.

To be certain, the Department of Justice has been forceful in articulating its normative justifications for prosecution in informational terms.<sup>44</sup> For example, in announcing Warner-Lambert’s payment of \$430 million to resolve criminal and civil charges brought against it, the Department announced: “This illegal and fraudulent promotion scheme corrupted the information process relied upon by doctors in their medical decision

---

fifteen years of testing from the submission of an Investigative New Drug application to the new drug’s delivery into the market (citing O’Reilly & Dalal, *supra*, at 304)).

44. See Peggy Chen, *Education or Promotion?: Industry-Sponsored Continuing Medical Education (CME) as a Center for the Core/Commercial Speech Debate*, 58 FOOD & DRUG L.J. 473, 473 (2003) (“‘It is after all, only within a particular information context that a drug really exists.’ . . . [D]rug information is the focus of many struggles between the Food and Drug Administration (FDA) and the pharmaceutical industry.” (quoting Richard T. Kaplar, *The FDA and the First Amendment*, in *BAD PRESCRIPTION FOR THE FIRST AMENDMENT: FDA CENSORSHIP OF DRUG ADVERTISING AND PROMOTION* 43, 50 (Richard T. Kaplar ed., 1993))).

making, thereby putting patients at risk.”<sup>45</sup> The Department has continued to make similar pronouncements in the years following the Warner-Lambert settlement, arguing that off-label promotion prevents patients from “know[ing] that their health care provider’s judgment has not been clouded by misinformation,”<sup>46</sup> or that “[o]ff-label marketing can undermine the doctor-patient relationship and adversely influence the clear judgment that a doctor’s patients have come to rely on and trust.”<sup>47</sup> In the latest record-breaking industry settlement, in which GlaxoSmithKline agreed to pay \$1 billion in criminal fines and \$2 billion in civil liabilities,<sup>48</sup> the government alleged that “[b]y misstating and exaggerating [the drug’s] efficacy . . . GSK misled the medical community about the risks and benefits” of the drug’s use in adolescents, an unapproved patient population.<sup>49</sup> The use of information is at the center of each of these allegations.

Given the government’s preoccupation with informational corruption, it seems strange that the law should care only about “the mouth of the promoter” and “not the ear or intent of the audience,”<sup>50</sup> but the two positions are only superficially at odds. Whereas tort law is concerned with causation, criminal law is concerned with an individual’s act and intent. Under the law of attempt, a criminal act willfully committed may be punished even where its illicit goal is not met.<sup>51</sup> But where the line

---

45. Press Release, U.S. Dep’t of Justice, Warner-Lambert To Pay \$430 Million To Resolve Criminal & Civil Health Care Liability Relating to Off-Label Promotion (May 13, 2004), *available at* [http://www.justice.gov/opa/pr/2004/May/04\\_civ\\_322.htm](http://www.justice.gov/opa/pr/2004/May/04_civ_322.htm).

46. Press Release, U.S. Dep’t of Justice, Eli Lilly and Company Agrees To Pay \$1.415 Billion To Resolve Allegations of Off-label Promotion of Zyprexa: \$515 Million Criminal Fine Is Largest Individual Corporate Fine in History; Civil Settlement Up To \$800 Million (Jan. 15, 2006), *available at* <http://www.justice.gov/opa/pr/2009/January/09-civ-038.html>.

47. Press Release, U.S. Dep’t of Justice, Novartis Pharmaceuticals Corp. To Pay More Than \$420 Million To Resolve Off-label Promotion and Kickback Allegations (Sept. 30, 2010), *available at* <http://www.justice.gov/opa/pr/2010/September/10-civ-1102.html>.

48. Whalen et al., *supra* note 10.

49. United States’ Complaint at 4, United States *ex rel.* Thorpe v. GlaxoSmithKline PLC, No. 11-10398-RWZ (D. Mass. Oct. 26, 2011).

50. United States v. Caronia, 576 F. Supp. 2d 385, 391–92 (E.D.N.Y. 2008) (rejecting defendant sales representative’s argument that he did not misbrand the drug within the meaning of 21 U.S.C. § 352(f) because he administered adequate warnings to a cooperating physician).

51. See Ira P. Robbins, *Double Inchoate Crimes*, 26 HARV. J. ON LEGIS. 1, 3 (1989) (“The inchoate crimes of attempt, conspiracy, and solicitation are well established in the American legal system. ‘Inchoate’ offenses allow punishment of an actor even though he has not consummated the crime that is the object of his efforts.”); Robert E. Wagner, *A Few Good Laws: Why Federal Criminal Law Needs a General Attempt Provision and How Military Law Can Provide One*, 78 U. CIN. L. REV. 1043, 1051 (2010) (arguing that the common law deemed it “unjust that defendants got away unpunished simply because they failed to complete their planned crimes”). It is not necessary to consider the question of whether there is such a crime as *attempted* misbranding because the object

between legitimate and illicit promotion is hard to define, or where minute and missing facts are needed to determine whether a manufacturer or its agents have transgressed that line, an inquiry into the “ear or intent of the audience”<sup>52</sup> might redound on that most elusive of legal concepts: *mens rea*.

Unlike adulteration, misbranding is not a strict liability offense—or at least the key elements of the offense call for a finding of knowledge.<sup>53</sup> A sophisticated defendant who harbors the intent to promote a drug for off-label use will seek the most effective means available to influence prescribing behavior. Herein lies the relevance of physicians’ learning habits and the informational pathways most often used by pharmaceutical and medical device companies to alter adoption and utilization rates, including for legitimate on-label promotion. An aberrant pattern of physician “detailing” by a sales force division, standing alone, may not be indicative of corporate intent; it might not even be indicative of the individual representative’s intent. On the other hand, a few isolated contacts between company personnel and key “opinion leaders” may very well be all the *actus reus* needed for a fact finder to infer an intent to misbrand a drug under § 331(a). *Res ipsa loquitur*: The marketing tactic speaks for itself.

---

offense itself covers such inchoate offenses as solicitation. Indeed, although § 331(a) seeks to prevent informational corruption, it criminalizes the affirmative steps taken toward that goal, so it is in effect its *own* attempt statute. *See* 21 U.S.C. § 331(a) (Supp. IV 2011).

52. *Caronia*, 576 F. Supp. 2d at 392.

53. As discussed in Part II.A, an offense under § 331(a) is determined by reference to the intended use of a drug as defined in 21 C.F.R. § 201.128, and that definition makes multiple references to “knowledge.” *See* 21 C.F.R. § 201.128 (2011). For example, intended use may be “shown by the circumstances that the article is, with the *knowledge* of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised.” *Id.* (emphasis added). Similarly, with respect to material omission, the regulation explains that “if a manufacturer *knows*, or has *knowledge* of facts that would give him notice” as to a change in intended use, it has an obligation to bring the label’s directions in line with that intended use. *Id.* (emphasis added). Both “knowingly” and “knew” have statutory definitions under the FD&C Act, and they are defined as, “with respect to information,” having “actual knowledge” or “act[ing] in deliberate ignorance or reckless disregard of the truth or falsity of the information.” 21 U.S.C. § 321(bb)(1)–(2) (2006). Subsection (bb)(2) seems to refer to the question of “defrauding” or “misleading,” but—without here getting into the contested issue of whether off-label promotion is misleading as a categorical matter—subsection (bb)(1) plainly refers to the use of the verb *to know* and the noun *knowledge* in 21 C.F.R. § 201.128. *Id.*

This Article advocates for the use of epistemological research as a means of discriminating among evidence of illicit off-label promotion and in constructing a theory of prosecution—or defense. Courts adjudicating False Claims Act suits have had experience in enumerating the ways in which the industry has effectuated its off-label promotional strategy. For example, the court in *United States ex rel. Duxbury v. Ortho Biotech Products, L.P.*<sup>54</sup> recounted the various illicit means employed by the defendant manufacturer: direct marketing to physicians, influencing the results of independent clinical trials—“Phase IV Marketing Trials”—rebate programs, and the use of kickbacks.<sup>55</sup> This last tactic was itself a multifaceted endeavor, with the defendant plying its product in return for discounts given to prescribing physicians, consulting fees, and advisory board honoraria, as well as cash.<sup>56</sup>

Taking the conduct in *Duxbury* as an example, one sees that marketing tactics, in the abstract, arrange themselves along a continuum of more or less suspect behavior. We could identify interference with independent clinical trials as more categorically suspect than the use of rebate programs, but that distinction is academic without a way of anchoring the particular marketing tactic within an informational context. How does the tactic relate to what the manufacturer was hoping to achieve? This is where a rudimentary understanding of physician behavior plays its role, with special attention to the diffusion of new medical information and the differences in adoption and utilization rates across different physician settings.

Although research on prescribing behavior and diffusion of medical knowledge has not been without conflicting results over the last three decades, there is consensus on a number of points relevant to the informational theory of off-label promotion. Physicians face serious challenges in assimilating new medical information,<sup>57</sup> and their ability to process new information relevant to treatment choices depends on a number of factors. These factors include a physician’s degree of specialization,<sup>58</sup>

---

54. *United States ex rel. Duxbury v. Ortho Biotech Prods., L.P.*, 579 F.3d 13 (1st Cir. 2009).

55. *Id.* at 17–18.

56. *Id.* at 19.

57. See generally Sandra H. Johnson, *Polluting Medical Judgment? False Assumptions in the Pursuit of False Claims Regarding Off-Label Prescribing*, 9 MINN. J.L. SCI. & TECH. 61 (2008) (criticizing causation theories implicit in False Claims Act suits for off-label promotion as misunderstanding the means by which physicians acquire the knowledge on which they base their treatment decisions).

58. See Lars Noah, *Medicine’s Epistemology: Mapping the Haphazard Diffusion of Knowledge in the Biomedical Community*, 44 ARIZ. L. REV. 373, 405 (2002) (speculating that “the growth in specialization by physicians . . . may improve their ability to absorb and critically appraise the new information” (footnote omitted)).

geographical setting,<sup>59</sup> professional status,<sup>60</sup> and whether a physician is part of a group practice, a network practitioner, or neither.<sup>61</sup> On the other hand, “marketing intensity” in itself has been shown by at least some studies to have no apparent relationship to adoption and utilization rates.<sup>62</sup> Something else must account for the past success of off-label promotion.

An analysis that begins with the assumption that the world of medicine may be divided into one of three major epistemological camps is an analysis doomed of its own artificiality from the start. But in order to be effective, sophisticated marketing must be tailored to known epistemological pathways. Therefore, an understanding of each is relevant here.

### B. The Customary Approach

Until recent decades, the standard for adopting new medical information was to rely on the opinions of renowned experts within a field or geographical area, rather than on clinical findings or profession-wide guidelines.<sup>63</sup> In theory, the customary approach values real-world

59. See generally John E. Wennberg, *Dealing with Medical Practice Variations: A Proposal for Action*, HEALTH AFF., Summer 1984, at 6 (contrasting interregional heterogeneity in medical practice with intraregional homogeneity).

60. See generally Mary A. Burke et al., *The Diffusion of a Medical Innovation: Is Success in the Stars?*, 73 S. ECON. J. 588 (2007) (studying the differential adoption and utilization rates of new coronary stent technology among “opinion leaders” and “non-star” physicians).

61. See generally Joel M. Schectman et al., *The Effect of an Education and Feedback Intervention on Group-Model and Network-Model Health Maintenance Organization Physician Prescribing Behavior*, 33 MED. CARE 139 (1995) (studying physician response to an HMO’s “academic detailing,” as measured by prescription behavior).

62. See Robyn Tamblin et al., *Physician and Practice Characteristics Associated with the Early Utilization of New Prescription Drugs*, 41 MED. CARE 895, 901 (2003) (measuring marketing intensity by reference to the number of detailing minutes and advertising pages). But see Robert Pear, *Fees to Doctors by Drug Makers To Be Disclosed*, N.Y. TIMES, Jan. 17, 2012, at A1 (claiming that a *Times* investigation found that “doctors who take money from drug makers . . . are more willing to prescribe drugs in risky and unapproved ways”).

63. See Johnson, *supra* note 57, at 76; Noah, *supra* note 58, at 382 (“Traditionally, when unsure about how to proceed, physicians would look to the judgments of ‘opinion leaders’ in their community for guidance . . .”); see also Sushil Bikhchandani et al., *Learning from the Behavior of Others: Conformity, Fads, and Informational Cascades*, J. ECON. PERSP., Summer 1998, at 151, 160 (“Social psychologists report that people imitate the actions of those who appear to have expertise.”). But see Oates, *supra* note 43, at 1279–80 (suggesting that the *Physicians’ Desk Reference* is the main source consulted by physicians when prescribing medicine).

experience over controlled studies,<sup>64</sup> casting doubt on the proposition that off-label prescribing is a consequence of direct-to-prescriber marketing efforts.<sup>65</sup> This skepticism is in keeping with more general studies on the ability of groups to assimilate new information and to cope with informational overload.<sup>66</sup> Under the “informational cascade theory,” individuals refrain from independent assessment of new alternatives as soon as the public pool of knowledge becomes “even modestly more informative than the signal of a single individual.”<sup>67</sup> It would, therefore, be cheaper for a physician to rely on community standards than to independently assess and adopt a manufacturer’s off-label claims.

Physicians possessing too limited a supply of time and resources to assess new clinical data prior to making treatment choices will rely both on their own—statistically insignificant—observations from practice and on the choices made by prior individuals who they know or otherwise trust as a source of information. If “indirect costs of innovation . . . inhibit adoption . . . when costs exceed [the] actor’s resource potential,”<sup>68</sup> then we can predict which physicians will be more likely to rely on the traditional approach of deferring to experts in the field. Given that tort law looks to the “standard of care” in determining liability in malpractice suits,<sup>69</sup> physicians with lower professional statuses will have good reason not to try the latest clinical innovation, especially if it is a decidedly off-label use.<sup>70</sup> Venturing into off-label uses without the backing of trendsetters in your area of expertise could lead to tort liability.<sup>71</sup>

---

64. See Johnson, *supra* note 57, at 73–75.

65. See *id.* at 73–74.

66. See generally Bikhchandani et al., *supra* note 63 (positing that informational cascades result from the propensity to imitate, an adaptation that allows individuals to take advantage of information accepted by a prior critical mass).

67. *Id.* at 155.

68. Barbara Wejnert, *Integrating Models of Diffusion of Innovations: A Conceptual Framework*, 28 ANN. REV. SOC. 297, 302 (2002).

69. See, e.g., *Robbins v. Footer*, 553 F.2d 123, 126 (D.C. Cir. 1977).

70. See Noah, *supra* note 58, at 394; see also Ann Lennarson Greer, *The State of the Art Versus the State of the Science: The Diffusion of New Medical Technologies into Practice*, 4 INT’L J. TECH. ASSESSMENT HEALTH CARE 5, 9 (1988) (“[T]he universal skepticism of practicing physicians regarding the utility of the scientific literature is startling.”). Query, however, whether Greer’s “universal skepticism” has not been rendered an overstatement in light of the EBM movement, which is thought to have gained considerable force since the publication of that article. See *infra* Part III.C.

71. However, at least one study has shown that the highest rates of new drug utilization were in drug categories exhibiting homogeneous efficacy where the new drugs in question showed little or no improvement over existing therapies. See Tamblyn et al., *supra* note 62, at 905. Although the study does not distinguish between on-label and off-label use, the results might suggest that nonleading physicians feel comfortable prescribing off-label in relatively stable areas, perhaps in response to lower prices or the availability of free samples. Cf. M.A. Morgan et al., *Interactions of Doctors with the Pharmaceutical Industry*, 32 J. MED. ETHICS 559, 561 (2006) (“Less than two-thirds

Knowing that the average physician looks to opinion leaders in making many treatment decisions, manufacturers will likely target key figures rather than “nonleading” physicians.<sup>72</sup> This hypothesis assumes both that certain types of physicians—general practitioners or general-practice pediatricians—are more likely to rely heavily on opinion leaders than other types—specialists—and that manufacturers would discriminate between types rather than promoting the off-label uses of its drugs to a broader cross section of professionals. The former assumption has already been discussed in this subpart.<sup>73</sup> As for the latter, it is fair to assume that the profit-maximizing approach would be to target only opinion leaders because that strategy is both more efficient and helps avoid regulatory detection. The government took note of this tactic in one company’s placement of off-label material on a password-protected website to which only “targeted, high-prescribing physicians” were given access.<sup>74</sup>

On this model of marketing behavior, documented instances of off-label promotion during a campaign of otherwise broad and uniform detailing<sup>75</sup> make for a weaker case of off-label promotion than the adoption of an off-label use by an opinion leader within a highly specialized field following formal contact with pharmaceutical agents. Whereas the latter may be probative of corporate *mens rea*, the former might be the result of efforts by a confused, incompetent, or self-interested sales representative. For example, in *Davico v. GlaxoSmithKline Pharmaceuticals, Inc.*,<sup>76</sup> the plaintiff admitted that he achieved the

---

(62.7%) selected ‘knowledge of the efficacy of the sample product’ as a reason for distributing free samples and 59.7% distributed samples to build a good relationship with the patient.”).

72. See Burke et al., *supra* note 60, at 589 (“[P]harmaceutical companies . . . target ‘opinion leaders’ in the medical community in their marketing efforts, on the assumption that adoption by such individuals will serve as an efficient engine for more widespread adoption of the drug . . .”).

73. See *supra* notes 63–67 and accompanying text.

74. Second Amended Complaint & Demand for Jury Trial at 10, *United States ex rel. Piacentile v. Cephalon, Inc.*, No. 03-6277 (E.D. Pa. Apr. 23, 2008) (“Cephalon has simply re-directed its strategy to keep it away from the FDA’s regulatory oversight.”).

75. Drug “detailing” refers to the practice of pharmaceutical sales representatives making office visits to physicians and other health care providers. See Noah, *supra* note 58, at 431.

76. *Davico v. GlaxoSmithKline Pharm.*, Civ. No. 05-6052-TC, 2007 WL 2984014 (D. Or. Oct. 9, 2007), *aff’d*, 2009 U.S. App. LEXIS 5153 (9th Cir. Mar. 10, 2009).

distinction of top promoter within his sales group by systematically promoting the drug Wellbutrin for off-label uses.<sup>77</sup>

The fear that an errant sales representative might place a pharmaceutical giant on the hook for criminal and civil enforcement actions, while consistent with a strict interpretation of modern American respondeat superior,<sup>78</sup> should be mitigated by the fact that actions *actually* brought by the government place great emphasis on the systematic targeting of opinion leaders. In *United States ex rel. Beilfuss v. Allergan, Inc.*,<sup>79</sup> a qui tam action brought under the False Claims Act and various state analogs on behalf of two relators, sixteen states, and the District of Columbia, the government enumerated the eighteen specific tactics used to promote Botox for off-label uses.<sup>80</sup> Four of these tactics dealt specifically with the opinion-leader phenomenon. These included use of “Regional Scientific Specialists” to help find appropriate physicians to “target” for off-label marketing efforts;<sup>81</sup> “use of physician speakers to pay them to influence other physicians to prescribe off-label”;<sup>82</sup> “the use of physicians as ‘key opinion leaders’ to influence other physicians”;<sup>83</sup> and recruiting doctors to be “traveling mentors” for the company’s “Physician Partnership Program.”<sup>84</sup> The overall “gravamen” of the claims was that Allergan had “developed and successfully executed a sophisticated marketing plan with the purpose of inducing physicians to prescribe the prescription drug . . . for . . . off-label uses (and off-label dosages).”<sup>85</sup>

Despite the supposed insistence on strict statutory bases for enforcement,<sup>86</sup> actual patterns of government enforcement seem to reflect the appreciation of an informational theory. For example, some commentators have noticed that the giving of gifts or other informal compensation is more likely to trigger serious investigation or prosecution<sup>87</sup> than arguably truthful detailing on off-label uses, which will likely only

---

77. *Id.* at \*2. Of course, the plaintiff also alleged that the manufacturer “actually expected, and even rewarded, off label marketing.” *Id.* Were his allegations otherwise, he would hardly have brought a qui tam action under the False Claims Act.

78. *See, e.g.,* *United States v. Hilton Hotels Corp.*, 467 F.2d 1000, 1004–07 (9th Cir. 1972).

79. *United States ex rel. Beilfuss v. Allergan, Inc.*, No. 08 CA 10305 RGS, 2008 WL 8081517 (D. Mass. Feb. 22, 2008).

80. Complaint ¶ 2, at 1–2, ¶ 34, at 8–11, *Beilfuss*, 2008 WL 8081517.

81. *Id.* ¶ 34(a), at 8.

82. *Id.* ¶ 34(h), at 10.

83. *Id.* ¶ 34(n), at 11.

84. *Id.* ¶ 34(p), at 11 (internal quotation marks omitted).

85. *Id.* ¶ 3, at 2.

86. *See* Osborn, *supra* note 12, at 326.

87. *See* Burroughs et al., *supra* note 12, at 573 (listing “payments to physicians” as one of “eight focal points of a typical off-label investigation”).

trigger warning letters.<sup>88</sup> If the customary approach still captures mainstream medical practice, then investigations that focus on ambiguous marketing to a broad audience should be less likely to result in formidable legal charges than investigations that hone in on certain access points of informational corruption.<sup>89</sup>

### C. The EBM Movement

Evidence-based medicine, a term first used in the 1990s,<sup>90</sup> describes the other major approach to incorporating new medical information into actual practice. The most widely accepted definition of EBM is the “conscientious, explicit, and judicious use of current best [scientific] evidence in making decisions about the care of individual patients.”<sup>91</sup> The social science and epistemological research discussed in the preceding subpart suggest that the rise of EBM is more aspirational than empirical.<sup>92</sup> On a more basic level, there is controversy as to the very nature of EBM and its relationship to other approaches.

Rather than set “best treatment” guidelines, EBM instructs physicians to turn to up-to-date clinical data and research findings to assess the course of treatment in each particular case. The method of assessing available medical evidence may vary with the peculiarities of a given practice, but there are at least two universal elements: (1) making certain that the assemblage of evidence is comprehensive, and (2) deciding how

---

88. See Paul D. Frederickson, *Criminal Marketing: Corporate and Managerial Liability in the Prescription Drug Industry*, 22 *MIDWEST L.J.* 115, 144–45 (2008). On the other hand, Frederickson suggests that this distinction is best explained by the government’s fear “of creating the justiciable controversy that establishes a clear precedent that truthful off-label promotion is constitutionally protected speech.” *Id.* at 144. Use of the antikickback statute as a basis for prosecution circumvents that thorny problem.

89. See Wejnert, *supra* note 68, at 300 (finding that “[m]edia becomes a channel of influence on adoption primarily when the innovations are popular, well-defined societal issues,” whereas “the spread of innovations with private consequences [including new medical practices] occurs largely due to spatial and temporal contiguity between a source of a new practice and a potential adopter”). *But see* Noah, *supra* note 58, at 438 (“New information may require multiple avenues of dissemination coupled with the passage of time before it sinks into the collective medical consciousness and alters prescribing behavior.”).

90. Caroline Young, *Medico-Legal Research Using Evidence-Based Medicine*, 102 *LAW LIBR. J.* 449, 452 (2010).

91. David L. Sackett et al., *Evidence-Based Medicine: What It Is and What It Isn’t*, 312 *BRIT. MED. J.* 71, 71 (1996).

92. See *supra* text accompanying notes 63–68.

to best structure the medical question meant to be answered by that evidence.<sup>93</sup> These clinical questions are often constructed according to the “PICO” mnemonic: (P) patient/problem/population, (I) intervention, (C) comparison, and (O) outcome.<sup>94</sup> As with the customary approach’s dipartite reliance on both personal clinical observation and received knowledge from opinion leaders, the informational theory of off-label promotion acts directly upon the structure of EBM learning.

Given that EBM reduces the prominence of personal clinical experience or knowledge acquired from colleagues,<sup>95</sup> my informational theory counsels for a different evaluation of off-label charges where EBM dominates. Rather than exercising overt influence over well-placed opinion leaders, manufacturers promoting their drugs for unapproved indications will focus on tactics such as inappropriately controlling independent clinical trials and exerting pressure upon the authors and editors of leading medical journals. However, the success of an off-label marketing strategy by the manufacturer need not involve the complicity of such individuals. Empirical surveys demonstrate that studies of new drugs funded by manufacturers tend to favor new treatments over the existing, approved alternatives.<sup>96</sup> Coupled with ambiguous indicia of an off-label marketing strategy, long-term relationships between clinical investigators and manufacturers might indicate an intent to exploit the evolving pathways of informational acquisition in the field of medicine that most closely corresponds to a target market for its drug.

Even where postapproval clinical trials of other indications or dosages are conducted under the auspices of FDA protocol, questions of fact may arise as to the manufacturer’s intent in carrying out those trials. Although the FDA often conditions final approval of an indication on the manufacturer’s commitment to conducting postapproval studies, the agency has never exercised its authority to withdraw its approval of an NDA as a consequence of a manufacturer’s failure to meet that

---

93. Young, *supra* note 90, at 452.

94. *Id.* at 456.

95. *See id.* at 451 (arguing that the current best scientific evidence component of EBM is what distinguishes it from “eminence-based medicine” (quoting John M. Eisenberg, *What Does Evidence Mean? Can the Law and Medicine Be Reconciled?*, 26 J. HEALTH POL. POL’Y & L. 369, 370 (2001))); *see also* Carter L. Williams, Note, *Evidence-Based Medicine in the Law Beyond Clinical Practice Guidelines: What Effect Will EBM Have on the Standard of Care?*, 61 WASH. & LEE L. REV. 479, 499 (2004) (“[A] significant difference between traditional practice and EBM is the reduced prominence of personal clinical experience.”).

96. Gary Edmond, *Judging the Scientific and Medical Literature: Some Legal Implications of Changes to Biomedical Research and Publication*, 28 OXFORD J. LEGAL STUD. 523, 536 (2008).

condition.<sup>97</sup> In past reports, the Office of Inspector General for the Department of Health and Human Services has expressed concern that FDA oversight of these so-called Phase IV trials was lax and hardly prioritized.<sup>98</sup> If the threat of NDA-withdrawal presents no deterrent effect, then those Phase IV commitments that *are* fulfilled might be evidence of something other than good-faith compliance.

Phase IV trials are sometimes referred to as “marketing trials” because their goal is to generate new information about an already-approved drug in the market. Under the informational theory of misbranding, this can either bolster a drug’s approved labeling or widen the gap between the label and its common usage. In any event, its significance to EBM is obvious. These tests produce the up-to-date information that stale Phase III results cannot provide. But the “marketing” appellation recognizes that much of the rationale behind satisfying an essentially nonbinding commitment is that it will promote the drug’s usage among both those writing prescriptions and those asking for them.<sup>99</sup> This was one of the relator’s chief allegations in the *Duxbury* case.<sup>100</sup> Although that claim was discarded in favor of the amended complaint’s allegations of direct physician kickbacks, the original complaint did allege that the defendant manufacturer “utilized ‘Phase IV Marketing Trials’ to, among other things, ‘encourage the physician, clinic, or hospital to use the drug in a way which [wa]s inconsistent with its FDA approved indications and administration methods.’”<sup>101</sup>

Because trials deemed to be Phase IV commitments are at least in theory conducted at the insistence of the FDA, it would be perverse to argue on the basis of their promotional effects alone that the manufacturer has committed an offense. Some other evidence must be marshaled to establish that the Phase IV trials were part of a corporate marketing scheme whose goal was to expand the common usage of an approved

---

97. See PETER BARTON HUTT ET AL., *FOOD AND DRUG LAW: CASES AND MATERIALS* 738 (3d ed. 2007).

98. *Id.*

99. See, e.g., Jamie L. Aldes, Note, *The FDA Clinical Trial Process: Effectuating Change in the Regulatory Framework Governing Clinical Trials To Account for the Historical Shift from “Traditional” to “New” Phase I Trials*, 18 *HEALTH MATRIX* 463, 472 (2008) (“Phase IV trials help to promote experiences with the drug to prominent physicians and the public through marketing.”).

100. See *supra* notes 54–56 and accompanying text.

101. *United States ex rel. Duxbury v. Ortho Biotech Prods. L.P.*, 579 F.3d 13, 17 (1st Cir. 2009) (alteration in original).

drug without investing the resources necessary to make a concomitant change in its label content. Short of that, the bare existence of Phase IV trials resulting in increased off-label use is nothing more than EBM properly at work.

The foregoing scenarios are ones in which, depending on the degree of pressure applied, the pharmaceutical defendant might be properly charged under statutes ancillary to § 331(a) of the FD&C Act. But the structure of EMB-inspired clinical questions also informs the types of off-label claims made by the defendant and thus speaks to the misbranding charges directly. Referring again to the PICO mnemonic, we find a number of opportunities for marketing to physicians who might aspire to the EBM approach, but who face the ordinary informational difficulties suggested above.

This seems to have been the strategy described by the allegations in *UFCW Local 1776 v. Eli Lilly & Co.*<sup>102</sup> First, the campaign shifted its focus from psychiatrists to primary-care physicians,<sup>103</sup> a less specialized field with a broader patient market and tighter time constraints per treatment decision, given the number of different ailments addressed by each primary-care physician. In accomplishing its marketing goals, Eli Lilly & Co. did the following: it suggested that, for middle-aged and elderly women (*Population*),<sup>104</sup> prescribing Zyprexa-olanzapine, a second-generation antipsychotic drug (SGA),<sup>105</sup> was an appropriate treatment (*Intervention*) as compared to the other SGA drugs on the market (*Comparison*)<sup>106</sup> for the alleviation of anxiety, mood disorders, and disrupted sleep patterns (*Outcome*).<sup>107</sup> The key to this strategy for off-label promotion is first to broaden the target audience from one that more routinely processes new medical information to one that must rely to a greater extent on the customary approach.

None of this detracts from the reality that EBM will be seen in most instances as an aid to FDA policy, or even as something that itself should be the object of protection,<sup>108</sup> rather than as another avenue for

---

102. *UFCW Local 1776 v. Eli Lilly & Co.*, 620 F.3d 121 (2d Cir. 2010).

103. *Id.* at 127.

104. *Id.* at 128.

105. *Id.* at 124.

106. *Id.* at 127.

107. *Id.*

108. *E.g.*, Second Amended Complaint at 7, *United States ex rel. Hopper v. Solvay Pharm., Inc.*, 590 F. Supp. 2d 1352 (M.D. Fla. 2008), *aff'd*, 588 F.3d 1318 (11th Cir. 2009) (No. 8:04-cv-2356-T-23TGW), 2007 WL 5118132 (“Off-label promotion diminishes the use of evidence-based medicine.”); Complaint ¶ 22, at 6, *United States ex rel. Beilfuss v. Allergan, Inc.*, No. 08 CA 10305 (D. Mass. Feb. 22, 2008), 2008 WL 8081517 (same); *see also* Second Amended Complaint and Demand for Jury Trial ¶ 24, at 7, *United States ex rel. Piacentile v. Cephalon, Inc.*, No. 03-6277 (E.D. Pa. Apr. 23, 2008) (“Permitting off-

misbranding. There is far less danger of informational corruption if physicians turn to the most recent medical evidence in making treatment choices. Indeed, one of the reasons that the FDA now allows the dissemination of reprints, albeit in a strictly guided fashion,<sup>109</sup> is that the agency acknowledges the lag in the broader profession's acquisition of new information published in journals.<sup>110</sup>

Despite EBM's perceived benefits from the lawyer-regulator's perspective, there is reason to believe that its advances among physicians are not significant enough to fully blunt the force of off-label promotion.<sup>111</sup> The nature of the concept itself has been criticized as reductionist and circular.<sup>112</sup> A hard EBM approach is impracticable because its application to real-life clinical settings involves a multitude of patient- and environment-specific considerations for which there is no research output.<sup>113</sup> Providing a label for the process of integrating "hard EBM" into the "real world" of patient care has thus been described as a bankrupt endeavor: it requires physicians to rely on a variant of the customary approach that hard EBM is supposedly meant to displace.<sup>114</sup>

In conclusion, the EBM phenomenon provides the government another informational damsel in distress to be protected through the prosecution of off-label promotion without affording drug manufacturers a criminal analog to what, at tort law, is known as the learned intermediary doctrine. That doctrine states the general proposition that a manufacturer does not

---

label promotion also removes incentives to obtain definitive clinical study data and weakens the goal of evidence-based medicine.”).

109. See generally U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: GOOD REPRINT PRACTICES FOR THE DISTRIBUTION OF MEDICAL JOURNAL ARTICLES AND MEDICAL OR SCIENTIFIC REFERENCE PUBLICATIONS ON UNAPPROVED NEW USES OF APPROVED DRUGS AND APPROVED OR CLEARED MEDICAL DEVICES (2009), available at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm>.

110. See J. Howard Beales III, *Economic Analysis and the Regulation of Pharmaceutical Advertising*, 24 SETON HALL L. REV. 1370, 1392–94 (1994) (pointing out symposia as an example of “other mechanisms to speed the diffusion of knowledge [about off-label uses]”).

111. See Ann MacLean Massie, Note, *In Defense of the Professional Standard of Care: A Response to Carter Williams on “Evidence-Based Medicine,”* 61 WASH. & LEE L. REV. 535, 550 (2004) (“EBM can be extremely helpful to clinicians as far as it goes, but the current circumstance is that it does not go very far. Because it is a fairly young movement, the number of medical questions for which there are current data developed according to principles of scientific methodology are quite limited.” (footnote omitted)).

112. See Mark Cook, *Evidence-Based Medicine and Experience-Based Practice—Clash or Consensus?*, 23 MED. & L. 735, 736 (2004).

113. See *id.*

114. See *id.* at 740; Massie, *supra* note 111, at 551.

have a common law duty to warn patients directly because physicians act as “learned intermediaries,” processing the manufacturer’s drug safety information and putting it to best use when writing prescriptions for their patients.<sup>115</sup> With respect to off-label promotion, EBM acts not as an independent filter granting manufacturers immunity from government enforcement but rather as the object of protection. The “filter” here consists of the more easily corrupted, traditional sources of medical knowledge. The informational theory posits that off-label promotion prevents EBM from delivering on its own promises.

#### D. Clinical Practice Guidelines

At first blush, clinical practice guidelines seem to occupy an intermediate position between the customary approach and EBM, but from the perspective of one engaging in off-label promotion, the access points look much the same as under the traditional regime of deferring to opinion leaders. One widely cited definition of CPGs is that they are “systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.”<sup>116</sup> CPGs suggest relatively up-to-date “best practices” for treatment decisions. CPGs are not dynamic in any true sense—either they reflect EBM at a given point in time or they reflect the accumulated judgment of experts in the field.<sup>117</sup> Both types of CPGs are content-

---

115. See, e.g., *Blain v. SmithKline Beecham Corp.*, 240 F.R.D. 179, 186 (E.D. Pa. 2007) (“In jurisdictions where the learned intermediary doctrine applies, [the defendant] may have no duty to warn individual users, depending on each individual plaintiff’s physician’s knowledge of the risks of prescribing [the drug] to [off-label] patients.”). A minority-jurisdiction exception to this rule provides that a manufacturer can be liable for failure to warn of the risks attendant in off-label use where that use accounts for a significant portion of that drug’s sales. *Id.* (citing *Miles Labs., Inc. v. Superior Court*, 184 Cal. Rptr. 98, 103 (Ct. App. 1982)). A conceptually related theory is that of “overpromotion,” whereby the manufacturer’s duty to warn arises from a saturation of the media with direct-to-consumer marketing, sometimes arguably for off-label uses. See *Salmon v. Parke, Davis & Co.*, 520 F.2d 1359, 1363 (4th Cir. 1975); *Perez v. Wyeth Labs. Inc.*, 734 A.2d 1245, 1253, 1257 (N.J. 1999); Amy D. White, Note, *The Mass Marketing of Prescription Drugs and Its Effect on the Learned Intermediary Doctrine*, 25 OKLA. CITY U. L. REV. 745, 750–51 (2000).

116. Arnold J. Rosoff, *Evidence-Based Medicine and the Law: The Courts Confront Clinical Practice Guidelines*, 26 J. HEALTH POL. POL’Y & L. 327, 328 (2001) (quoting COMM. TO ADVISE THE PUB. HEALTH SERV. ON CLINICAL PRACTICE GUIDELINES, INST. OF MED., CLINICAL PRACTICE GUIDELINES: DIRECTION FOR A NEW PROGRAM 38 (Marilyn J. Field & Kathleen N. Lohr eds., 1990)).

117. See Noah, *supra* note 58, at 418.

based and should therefore be thought of as being fundamentally distinct from a true EBM approach, which is process-based in nature.<sup>118</sup>

Although the use of CPGs reduces physicians' reliance on statistically insignificant observations from their own practices, the default point of departure for many CPGs remains the same as under the traditional approach—the “imminence-based” medicine expounded by opinion leaders. In prosecuting a case of off-label promotion, the government will find its most relevant evidence in the relationship between industry and key opinion leaders, as well as the relationship between industry and the purveyors of CME seminars. CME seminars help establish the quantum of consensus necessary to have a treatment plan adopted in a CPG and are thus at least indirectly a key type of diffusion point for medical knowledge. In the late 1980s, the pharmaceutical industry began to realize the potential of turning this diffusion point into an access point, and by the next decade, Congress was conducting hearings on the effects of this relationship.<sup>119</sup>

There is no central body that produces CPGs the way the American Law Institute produces the Restatements of the Law, so there are often competing “best practices” identified by “rival” guidelines. Some have suggested that lawyers might find it useful to distinguish between the CPGs based on EBM and those based on communal standards of practice.<sup>120</sup> The great variety of CPGs allows the government and defendants in misbranding prosecutions to use the distinction as a tool in assessing evidence of off-label promotion. Both the approved use of a drug and the off-label use for which it was allegedly promoted will be known, so the universe of relevant CPGs will necessarily be a finite one. If the CPGs that happen to recommend that class of drug for that off-label use are of the “EBM type,” the defendants can defend against circumstantial evidence that they influenced experts individually or through CME seminars. If the targets of the alleged marketing scheme practice in a field operating under an influential EBM-based CPG, defendants in that

---

118. *But see* Rosoff, *supra* note 116, at 328 (“Because CPGs are the most common practical embodiment of EBM, the terms . . . have often been used interchangeably [by some commentators] . . .”).

119. 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, 155 (2007).

120. *See* Rosoff, *supra* note 116, at 329.

case would also have something similar to a negative causation defense in civil False Claims Act suits.

So how do we put all of this together? As an analytical approach, the informational theory seems better suited to the crafting of regulatory guidelines and safe harbors than to the prosecution of crime. The preceding discussions have at times assumed that particular medical fields are dominated by a single epistemological approach to the adoption and utilization of new information, but off-label promotion will often entail the marketing of a single drug to variegated, sometimes unexpected, medical fields. The informational theory, then, is not a panacea for shoring up doctrinal bedrock, but it accomplishes at least three things: it rationalizes and communicates the essence of the misbranding offense; it could inform the FDA's development of "best practices" guidelines for industry with respect to marketing and the compilation and dissemination of scientific data; and it could serve as an evidentiary tool in the hard cases of ambiguous marketing behavior.

#### IV. THE INSTITUTIONAL THEORY

##### A. *The Normative Framework*

The institutional theory of off-label promotion essentially asks whether the defendant has a license—an application—for introducing a new drug use into the market.<sup>121</sup> It is not interested in medical epistemology or the widening gap between common usage and approved indications. Whereas the informational theory informs the intellectual underpinnings of the misbranding offense, exposing exceptions that are mutually beneficial to regulators and industry alike, the institutional theory is concerned with circumvention of the regulatory process as a categorical matter. In effect, its concern is with affronts to regulatory authority. In that respect, the institutional theory is not, to put it colloquially, "the softer side of Sears."

Like the relationship between state sovereign immunity and the Eleventh Amendment, the institutional theory of off-label promotion and § 331(d) are of a piece; yet the former is far more extensive than the latter. In making it a violation for manufacturers or their agents to promote a drug use without having obtained a proper NDA, the statute pinpoints the specific *actus reus* of the violation, but does not elaborate much on the actor's intent or the philosophy behind the prohibition. Why should prosecutors resort to this seemingly inferior normative ground for prosecution? Would not normative arguments resting on the

---

121. See 21 U.S.C. § 331(d) (Supp. IV 2011); see also *supra* Part II.B.

concerns of the informational theory make for a stronger normative case, and, by way of publicity, have a stronger deterrent effect? I propose three broad explanations for why the institutional theory of prosecution might be emphasized.

First, the primary challenges posed by off-label promotion in the real world are not sufficiently addressed by the letter of the FD&C Act or its related regulations.<sup>122</sup> Off-label promotion is more often accomplished through in-person contact, instead of by way of the printed material that is more easily subjected to regulatory scrutiny. Moreover, even if nonprint advertising were as easy to regulate as its textual counterpart, the sponsoring of CME seminars or the dissemination of medical journal reprints are afforded a certain measure of First Amendment protection, even under the commercial speech doctrine. So many means of communication fall through the various cracks of the FD&C Act's scheme—either because of the impossibility of fully regulating the field or because of the gaps imposed by higher law.

Even where the same evidence discussed in the preceding Parts of this Article could be as useful under § 331(d) as under § 331(a), the penalties provided by the FD&C Act do not provide enough of a deterrent effect on their own to keep profit-maximizing firms from approaching off-label marketing as a cost-benefit proposition. Even where the threat of a felony conviction or a debarment proceeding is actually posed, a pharmaceutical company could restrict liability to a lesser subsidiary and thus insulate itself from the fullest effect of either harsh penalty.<sup>123</sup> The institutional theory of prosecution informs the use of statutes that act at higher levels of generality and carry weightier penalties, most importantly, the general conspiracy statute, discussed in the next subpart.<sup>124</sup>

Second, it is likely that many off-label prosecutions begin at the U.S. Attorneys' Offices rather than at the FDA, and federal prosecutors are less likely to be interested in the nuances of informational theory than with the frustration of a governmental scheme. The timing of large-scale settlements between prosecutors and the pharmaceutical companies indicates that many matters begin with a whistleblower's filing of a qui

---

122. See HUTT ET AL., *supra* note 97, at 541–42 (“The primary problems posed by advertising for prescription drugs, however, do not appear easily redressable by the authority to issue regulations or, indeed, to invoke the formal enforcement sanctions provided by the FD&C Act.”).

123. The FDA has not debarred a single firm since 1993. *Id.* at 1333.

124. See *infra* Part IV.B.

tam action under the False Claims Act. Some of the most significant such cases—*United States ex rel. Rost v. Pfizer, Inc.*<sup>125</sup> and *Duxbury*,<sup>126</sup> for example—involved former corporate officers. Those cases where the plaintiffs met with less success—such as *United States ex rel. Hopper v. Solvay Pharmaceuticals, Inc.*<sup>127</sup> and *Davico*<sup>128</sup>—involved sales representatives. The latter arguably have greater firsthand experience with the sort of conduct prohibited as a misbranding offense under § 331(a), but the former necessarily possess greater information about broader corporate activities and marketing plans. A criminal case can be built on this latter set of evidence with far less need for the scientific expertise possessed by the FDA. By contrast, the informational approach discussed above requires far more sophisticated knowledge of drug categories and usages. It makes sense to expect that large criminal settlements in the pharmaceutical industry will be accompanied by the civil settlement of this former type of False Claims Act suit.

This foregoing reason for emphasizing the institutional theory relies on a sometimes unfair assumption of lesser expertise on the part of federal prosecutors. Although this might generally be the case, given that Assistant U.S. Attorneys are generalists who might handle the prosecution of any federal offense, recent history illustrates that the prosecution of off-label promotion has been largely based out of two offices: the U.S. Attorney's Office for the Eastern District of Pennsylvania in Philadelphia, and the U.S. Attorney's Office for the District of Massachusetts in Boston.<sup>129</sup> With the concentration of FDA-related caseloads in a small number of offices, federal prosecutors there will necessarily develop an in-depth expertise borne of experience. In fact, as early as the 1950s there were U.S. Attorneys' Offices that dedicated a certain segment of their corps to prosecuting FDA-related offenses.<sup>130</sup>

---

125. *United States ex rel. Rost v. Pfizer, Inc.*, 507 F.3d 720, 723 (1st Cir. 2007) (stating that relator was the vice president of marketing for defendant Pfizer).

126. *United States ex rel. Duxbury v. Ortho Biotech Prods., L.P.*, 579 F.3d 13, 16 (1st Cir. 2009) (stating that relators were a regional key account specialist and territory manager for the defendant manufacturer).

127. *Hopper v. Solvay Pharm., Inc.*, 590 F. Supp. 2d 1352, 1354 (M.D. Fla. 2008), *aff'd*, 588 F.3d 1318 (11th Cir. 2009).

128. *Davico v. GlaxoSmithKline Pharm.*, Civ. No. 05-6052-TC, 2007 WL 2984014, at \*2 (D. Or. Oct. 9, 2007), *aff'd*, 2009 U.S. App. LEXIS 5153 (9th Cir. Mar. 10, 2009).

129. *E.g., In re Neurontin Mktg., Sales Practices & Prods. Liab. Litig.*, 618 F. Supp. 2d 96, 104 (D. Mass. 2009); *United States ex rel. Duxbury v. Ortho Biotech Prods., L.P.*, 551 F. Supp. 2d 100 (D. Mass. 2008), *aff'd in part and rev'd in part*, 579 F.3d 13 (1st Cir. 2009); *United States ex rel. Rost v. Pfizer Inc.*, 446 F. Supp. 2d 6 (D. Mass. 2006), *aff'd in part and rev'd in part*, 507 F.3d 720 (1st Cir. 2007).

130. *See Hearing on H.R. 15315 Before the Subcomm. on Pub. Health and Env't of the H. Comm. on Interstate and Foreign Commerce*, 92d Cong. 46 (1972) (statement of Stephen Kurzman, Assistant Secretary, U.S. Department of Health, Education and Welfare) (describing the Manhattan U.S. Attorney's Office as possessing, during his

Third, and perhaps most importantly, the government believes that off-label promotion represents a harm beyond the misbranding offense itself. This affront to regulatory authority poses a threat not only to the public as a collective of patients but also to the government as a collection of agencies. In other words, prosecution serves as the backstop that makes more nuanced regulation and enforcement possible in the first place. Without blunt deterrence, the mandatory nature of our current food and drug regime would be tarnished. Under this theory, then, off-label promotion implicates three larger concerns: the rule of law, the relationship between regulators and regulated industry, and the financial interests of the government to the extent that it acts as a health care manager. These concerns extend far beyond the narrower interests of the FDA, and so federal prosecutors will not feel tethered to the nuanced theories espoused by that agency's own scheme.

Of course, the evidence discussed in the preceding Part does not become irrelevant under an institutional theory of prosecution. After all, most prosecutions charge the defendant under both § 331(a) and § 331(d). Where a certain marketing tactic or other conduct is ambiguous, looking at the circumstantial evidence provided by its context is still important. But to the extent that certain evidence is determined to be probative of off-label promotion, the weakness of its effect upon the medical profession will probably not play much of a mitigating role in the prosecutors' exercise of discretion. The offense here is to the FDA as an institution and as an arm of the U.S. government, not to the public or to the medical profession directly. The government routinely expresses this conclusion in its press releases accompanying massive settlements: off-label promotion "undermines the FDA's role in protecting the American public,"<sup>131</sup> or "undermine[s] the drug approval process,"<sup>132</sup> and, importantly, "also costs the government billions of dollars."<sup>133</sup> For the government, this final line of reasoning is another advantage of the institutional theory.

---

time there in the 1950s and 1960s, a team of prosecutors dedicated exclusively to handling FDA-related cases).

131. U.S. Dep't of Justice, *supra* note 46 (internal quotation marks omitted).

132. Press Release, U.S. Dep't of Justice, Pharmaceutical Companies To Pay \$214.5 Million To Resolve Allegations of Off-Label Promotion of Zonegran (Dec. 15, 2010) (internal quotation marks omitted), *available at* <http://www.justice.gov/opa/pr/2010/December/10-civ-1444.html>.

133. *Id.* (internal quotation marks omitted).

## B. *Off-Label Promotion as a Conspiracy To Defraud the United States*

Of all the sections found in Title 18 of the United States Code, few must be as attractive to those prosecuting off-label promotion<sup>134</sup> as § 371, and in particular the defraud clause of this general conspiracy statute.<sup>135</sup> But the defraud clause of § 371 is as beguiling as it is attractive, and courts have wrestled with its meaning even in matters that are prosecuted frequently in open court. As applied to off-label promotion, the ultimate question is whether the manufacturer conspired with others to defraud the United States by interfering with the operation of the FDA's regulatory scheme. The line between the text of § 371 and this reading of the defraud clause, however, has been somewhat unsteady and, without the right formulation, its application to the facts of an off-label case can be unclear.

In this subpart, I begin by discussing the text of § 371 along with the Supreme Court's early interpretation of the statute, which is still routinely cited. Because off-label promotion is an offense that strays far from common law conceptions of fraud, I focus on the application of § 371 to cases in which the government has not suffered a pecuniary loss. Finally, I suggest that the proper inquiry as to off-label promotion should be whether a drug manufacturer has interfered with the FDA's function by undermining the drug approval process. Throughout, I will be referring to common means of off-label promotion in order to illustrate which marketing practices can be reached by each of the various formulations and those which cannot. Particular attention will be given to the "hard case" of truthful off-label promotion.

### 1. *Statutory Background*

Section 371 makes it a crime to "conspire *either* to commit any offense against the United States, *or* to *defraud* the United States, or any agency thereof in any manner or for *any* purpose," where "such persons

---

134. To review: Although *off-label promotion* is a term not itself found in the FD&C Act, its prohibition is embodied in a number of statutory and regulatory provisions operating together. See 21 U.S.C. § 331(a) (Supp. IV 2011) (prohibiting the "introduction into interstate commerce of any . . . drug . . . that is adulterated or misbranded"); *id.* § 352(f) (defining a drug as "misbranded" if its labeling does not bear "adequate directions for use"); 21 C.F.R. § 201.5 (2011) (defining "*adequate directions for use*" as directions "under which the layman can use a drug safely and for the purposes for which it was intended"); *id.* § 201.128 (providing that "*intended use*" is evidenced by "labeling claims, advertising matter, or oral or written statements" by manufacturers or their representatives). For a discussion of how these provisions operate in tandem, see *United States v. Caronia*, 576 F. Supp. 2d 385, 389 n.2 (E.D.N.Y. 2008).

135. See 18 U.S.C. § 371 (2006).

do *any* act to effect the object of the conspiracy.”<sup>136</sup> Whereas the offense clause provides a conspiracy charge for those whose object is some other federal crime, the text of the defraud clause contemplates a substantive offense. Although the statute limits the punishment for conspiracies to commit a misdemeanor at the maximum punishment provided for the object crime, the substantive crime of conspiring to defraud the United States is not similarly capped.<sup>137</sup> This distinction makes charging the latter type of conspiracy an especially compelling option for prosecutors.<sup>138</sup>

Aside from the proposition that the defraud clause creates its own substantive offense not subject to misdemeanor limitations, little else about this section’s interpretation flows ineluctably from the text. And, rather than read § 371 against a common law background, courts long ago established that the defraud offense meant something more expansive than fraud at common law.<sup>139</sup> The most important difference between common law fraud and the federal defraud offense is that the latter need not implicate a pecuniary interest.<sup>140</sup>

To this day, the touchstone formulation for this offense is the one laid down in *Hammerschmidt v. United States*.<sup>141</sup> There, the Court held that to defraud “means to interfere with or obstruct one of [the government’s] lawful governmental functions by deceit, craft, or trickery, or at least by means that are dishonest.”<sup>142</sup> So as not to imbue its definition with too strict a meaning, the *Hammerschmidt* Court clarified that this illicit purpose to obstruct or interfere meant “only that [the government agency’s]

136. *Id.* (emphasis added).

137. *See id.* (punishing conspiracies against the United States as felonies, unless the goal of the of conspiracy is merely a misdemeanor).

138. *See* Pamela H. Bucy, *Crimes by Health Care Providers*, 1996 U. ILL. L. REV. 589, 629 (“The choice [between clauses] makes a difference when the federal offense which the defendants allegedly conspired to violate is a misdemeanor . . . . The same conspiracy, charged under the ‘defraud’ provision, ensures that the punishment is a felony.”).

139. *Dennis v. United States*, 384 U.S. 855, 861 (1966) (“It has long been established that this statutory language is not confined to fraud as that term has been defined in the common law.”).

140. Although many opinions of more recent vintage can be cited for this proposition, *see, e.g.*, *United States v. Masquelier*, 210 F.3d 756, 758 (7th Cir. 2000), the First Circuit stated the proposition dramatically more than one hundred years ago. In *Curley v. United States*, the court explained that, “[a]s a moral offense, defrauding the government of its right and its facilities for rendering a proper service to the people . . . cuts deeper than defrauding the government of a wheelbarrow.” 130 F. 1, 9 (1st Cir. 1904).

141. *Hammerschmidt v. United States*, 265 U.S. 182 (1924).

142. *Id.* at 188.

legitimate official action and purpose shall be defeated by misrepresentation, chicane or the overreaching of those charged with carrying out the governmental intention.”<sup>143</sup> Relying on this famous reading of the defraud clause, courts concluded that the statute did not require that the means used to achieve the unlawful goal of the conspiracy be themselves unlawful.<sup>144</sup> With such a broad interpretation, courts and commentators have struggled to apply and define § 371 correctly without unintentionally criminalizing legitimate behavior.<sup>145</sup>

Where, as with off-label promotion, the conspiracy<sup>146</sup> has as its object something other than depriving the government of its property, the focus has been on the conspirators’ intentional “interference” with or “obstruction” of a governmental function.<sup>147</sup> Of course, such interferences or obstructions necessarily vary according to the governmental function in question.<sup>148</sup> As a consequence, applying one line of interference

---

143. *Id.*

144. *See, e.g.,* United States v. Turkish, 623 F.2d 769, 771 (2d Cir. 1980); *see also* Christian Davis & Eric Waters, *Federal Criminal Conspiracy*, 44 AM. CRIM. L. REV. 523, 530 (2007) (“Virtually any method used to defraud the United States will suffice for the purposes of the statute.”). In addition to resting upon the traditional *Hammerschmidt* passage, this interpretation is supported by the text of the statute, which translates the common law “overt act” requirement as “any act to effect the object of the conspiracy.” 18 U.S.C. § 371 (2006) (emphasis added).

145. *Compare* United States v. Goldberg, 105 F.3d 770, 775 (1st Cir. 1997) (“[T]he defraud clause of section 371 has a special capacity for abuse because of the vagueness of the concept of interfering with a proper government function.”), with Abraham S. Goldstein, *Conspiracy To Defraud the United States*, 68 YALE L.J. 405, 428 (1959) (“[I]t was necessary to leave the definition as open-ended as the functions of government in an expanding society.”).

146. There is an exception “to the applicability of the intracorporate conspiracy doctrine,” under which intracorporate agents lack the requisite multiplicity to form a conspiracy, “for intracorporate criminal conspiracies arising under 18 U.S.C. § 371.” *McAndrew v. Lockheed Martin Corp.*, 206 F.3d 1031, 1038 (11th Cir. 2000); *see also* United States v. Peters, 732 F.2d 1004, 1008 (1st Cir. 1984) (“The actions of two or more agents of a corporation, conspiring together on behalf of the corporation, may lead to conspiracy convictions of the agents . . . and of the corporation . . .”); United States v. Caronia, 576 F. Supp. 2d 385, 403 (E.D.N.Y. 2008) (“[A] corporation may conspire with its own agents, officers, and employees in violation of 18 U.S.C. § 371.” (citing United States v. Hartley, 678 F.2d 961, 972 (11th Cir. 1982), *overruled on other grounds*, United States v. Goldin Indus., 219 F.3d 1268 (11th Cir. 2000))). In addition to conspiracies among corporate officers for which the corporation may be held liable, a drug manufacturer might conspire with the sales agencies it charges with handling its drug marketing. *See McAndrew*, 206 F.3d at 1038.

147. Goldstein, *supra* note 145, at 438–39 (collecting cases and describing this category as, “of course, the one which has caused the greatest difficulty”).

148. *See generally* Brian Rubens, Comment, *Common Law Versus Regulatory Fraud: Parsing the Intent Requirement of the Felony Penalty Provision of the Food, Drug, and Cosmetic Act*, 72 U. CHI. L. REV. 1501 (2005). Rubens argues that, in what he calls “focused” fraud statutes—as opposed to the mail fraud and wire fraud statutes—the “structure and purpose” of the background regulatory statutes provide specific frameworks within which to identify and punish fraud. *Id.* at 1525. Although he does

decisions to disparate regulatory contexts can prove not easy. The most prominent line of interference decisions relies on the Second Circuit's opinion in *United States v. Klein*,<sup>149</sup> a tax prosecution. Although I later argue in favor of a formulation more amenable to the peculiarities of the misbranding offense, the *Klein* doctrine serves an important role in the examination of § 371 because it is well developed.

## 2. Klein Conspiracies

The *Klein* opinion itself gives little form to the interference concept, but it has nonetheless lent its name to the so-called *Klein* conspiracy.<sup>150</sup> In *Klein*, the defendants were accused of “running an immense whiskey selling business in a fashion calculated to minimize the amount of United States income tax they would have to pay,”<sup>151</sup> and charged with “conspiring to defraud the United States by impeding, impairing, obstructing and defeating the lawful functions of the Department of the Treasury in the collection of the revenue.”<sup>152</sup> In upholding the convictions, the Second Circuit found that the evidence appeared “directly in line” with the crime as defined by the “deceit, craft, or trickery” formulation in *Hammerschmidt*, and reiterated that the defraud offense is not limited to “the cheating of the Government out of property or money.”<sup>153</sup>

Whatever the limitations of the *Klein* opinion, its progeny have established the baseline rule that evidence of an interference conspiracy must prove that impeding the agency was one of the intended objects of the crime, and “not merely a foreseeable consequence or collateral effect.”<sup>154</sup> But to be found guilty of impeding an agency's function, the interference or obstruction “need not be an objective that is sought as an end in itself.”<sup>155</sup> The analogy to off-label promotion seems straightforward:

---

not categorize § 371 as a focused fraud statute, one must necessarily look at the structure and purpose of an agency's organic statute in order to answer whether a defendant has interfered with the agency's operation.

149. *United States v. Klein*, 247 F.2d 908 (2d Cir. 1957).

150. *See, e.g.*, *United States v. Tucker*, 419 F.3d 719, 720 (8th Cir. 2005) (referring to a conspiracy to defraud the United States by impeding the assessment and collection of income tax as a “so-called *Klein* conspiracy”). Like *Tucker*, the vast majority of cases deemed to be *Klein* conspiracies have involved elaborate tax evasion schemes.

151. *Klein*, 247 F.2d at 911.

152. *Id.* at 915 (internal quotation marks omitted).

153. *Id.* at 916.

154. *E.g.*, *United States v. Gricco*, 277 F.3d 339, 348 (3d Cir. 2002).

155. *Id.*

The promotion of a drug for an indication not approved by the FDA is intended both to bypass the costly new use approval process and to circumvent the strict guidelines by which manufacturers and their sales representatives may legitimately discuss off-label uses. That the ends sought are increased profits rather than regulatory obstruction does nothing, on its own, to undermine the § 371 charge brought against the manufacturer or its sales representatives.

But not all instances of off-label promotion will satisfy the prosecution's evidentiary burden under the *Klein* doctrine. Because most courts have grafted a concealment element into the doctrine, even brazen promotion for unapproved indications may fall outside the *Klein* rubric. In *United States v. Gricco*, the Third Circuit drew a fine line between evidence of passive frustration and that of active concealment. According to that court, evidence that the conspirators did not report their illicit income was "plainly not enough" to show an objective to impede the IRS, but evidence that the defendant told other participants to store their illicit income in safes within their homes, rather than depositing the money in their bank accounts, was sufficient to sustain a conviction.<sup>156</sup>

To illustrate the gap between the *Klein* doctrine and the misbranding offense, consider the act of verbally promoting a drug for an unapproved indication. Suppose that the leading medical compendia recognize the drug as having a therapeutic value in the treatment of that indication, thereby qualifying this particular usage for reimbursement under Medicare and Medicaid.<sup>157</sup> If a drug manufacturer were to encourage its sales representatives to discuss this coverage and other supporting medical literature with physicians, there would be a violation of the FD&C Act regardless of concealment.<sup>158</sup> The same might be said, albeit less persuasively, of ambiguous materials suggestive of treatments for which FDA approval is lacking.<sup>159</sup> But without at least a modicum of

---

156. *Id.* at 348–49.

157. See 42 U.S.C. § 1396r-8(k)(6) (2006) (permitting reimbursement for any drug usage approved by the FDA or included in certain pharmacological compendia); *United States ex rel. Rost v. Pfizer, Inc.*, 507 F.3d 720, 723 n.1 (1st Cir. 2007) (“[R]eimbursement is available for certain off-label uses that are medically ‘essential’ or recognizable within one of several medical compendia.” (quoting 42 U.S.C. § 1396r-8(k)(6))).

158. See 21 U.S.C. § 333(a)(1) (2006) (providing that a violation of the misbranding provisions of § 331 is punishable as a misdemeanor); *id.* § 333(a)(2) (providing that a violation of § 331 is punishable as a felony after a prior conviction under § 333 has become final, or where the violation was committed “with the intent to defraud or mislead”).

159. *Cf. UFCW Local 1776 v. Eli Lilly & Co.*, 620 F.3d 121, 127–28, 135–36 (2d Cir. 2010) (describing, in a False Claims Act case, the defendant's promotional materials, which focused on symptoms that are characteristic of a variety of indications, not all of which the defendant's drug was approved to treat).

concealment or evasion, this marketing would not be brought within the *Klein* rubric. Indeed, even the hallmark *Hammerschmidt* formulation seems to fall short. These illustrations suggest that the concealment element incorporated into § 371 by the *Klein* progeny is in large part a byproduct of the underlying tax evasion schemes at work in those cases.

Although the prosecution of truthful but illicit marketing necessitates an alternative formulation of § 371, enforcement actions of this sort are probably far outnumbered by criminal investigations focusing on marketing practices easily squared with the *Klein* doctrine.<sup>160</sup> When engaged in off-label promotion, pharmaceutical companies and the sales agencies with which they contract are likely to obscure their tactics. For example, in the seminal case of *United States ex rel. Franklin v. Parke-Davis*,<sup>161</sup> the government alleged that the defendant's officers concealed its marketing activity by shredding internal documents and by encouraging sales representatives not to leave "paper trail[s]" of their physician visits.<sup>162</sup> The government fired similar allegations at GlaxoSmithKline, claiming that it "took steps to evade detection by government agencies and conceal the real purpose and nature of activities, . . . concealing the documents that demonstrated the conduct."<sup>163</sup> In *United States v. Ballistrea*,<sup>164</sup> an individual prosecution involving a far less prominent manufacturer, the government alleged that the defendant instructed the recipients of its promotional material to hide the literature sent to them.<sup>165</sup> This conduct would satisfy the *Klein* formulation without more. As explained by the *Ballistrea* court, "such evidence of active concealment and evasion is more than sufficient" to prove that defendants impeded the "FDA's lawful function of regulating the marketing and distribution of medical devices and drugs."<sup>166</sup>

---

160. See Frederickson, *supra* note 88, at 144 (arguing that the government is "less likely to prosecute based solely on truthful off-label promotion" and would instead "send warning letters and make other threats of legal action").

161. *United States ex rel. Franklin v. Parke-Davis*, 147 F. Supp. 2d 39 (D. Mass. 2001).

162. *Id.* at 46 (internal quotation marks omitted).

163. Complaint at 20, *United States ex rel. Thorpe v. GlaxoSmithKline PLC*, No. 11-10398-RWZ (D. Mass. Oct. 26, 2011).

164. *United States v. Ballistrea*, 101 F.3d 827 (2d Cir. 1996).

165. *Id.* at 833.

166. *Id.*

### 3. *The Regulated Benefits Formulation*

Despite the hoary proposition that the defraud clause is in derogation of the common law, courts have seen fit to import into § 371 language reminiscent of so many common law concepts—misrepresentation and deceit chief among them. These concepts, sounding in the common law of fraud, have led courts to strained formulations of the offense where simpler rules could have obtained. The following rule explains cases in which § 371 convictions were upheld despite the lack of any pecuniary loss to the government: Parties who engage in transactions covered by a comprehensive regulatory scheme have a duty not to undermine the objectives of that scheme, and to do so is to defraud the administering agency. The mission of each agency informs what it means to undermine its objectives. In the FDA context, benefiting from practices reserved for those in compliance with the drug approval scheme undermines the agency's fundamental objectives in regulating prescription drugs.

A regulated benefits formulation demystifies the notion that an unlawful scheme can be perpetrated through entirely lawful acts. It also explains the outcomes of non-pecuniary-loss cases. Moreover, because it looks to governing rules and regulations as the source of the parties' duties, it helps anchor the defraud clause of § 371 in the specific context within which an offense is committed.<sup>167</sup> A manufacturer seeking to introduce a new drug into interstate commerce agrees to participate in a comprehensive regulatory scheme replete with myriad regulations, guidelines, and safe harbors. Under the regulated benefits formulation, no showing of misrepresentation or trickery is necessary for a § 371 charge to be sustained against those who interfere with the FDA's prescription drug scheme by rendering its approval and labeling requirements less meaningful.

One entity's participation in a federal scheme often deprives another entity of some resulting benefit, such that corruption by current participants interferes with the scheme's legitimate goals in a way that defrauds the agency. In both *United States v. Gallup*<sup>168</sup> and *United States v. Barker Steel Co.*,<sup>169</sup> for example, the defendants conspired to obtain for themselves contracts that, under the relevant program's guidelines, should have

---

167. See generally Goldstein, *supra* note 145. Although Goldstein's chronicling of the federal conspiracy law's development through the mid-twentieth century ultimately yields another multipronged test employing common law concepts, he did recognize that "[r]egulations and customs as well as statutes furnished standards of duty and obligation." *Id.* at 427. He viewed these standards as relevant, given that "there would be no conspiracy to defraud the United States if defendants had agreed to do only that which the law allowed." *Id.* (internal quotation marks omitted).

168. *United States v. Gallup*, 812 F.2d 1271 (10th Cir. 1987).

169. *United States v. Barker Steel Co.*, 985 F.2d 1123 (1st Cir. 1993).

gone to other entities. In *Gallup*, the defendant was tasked with securing approval from the Department of Housing and Urban Development (HUD) for a local project in return for a share of the finder's fee received by his coconspirator.<sup>170</sup> Although the government did not suffer any pecuniary loss and such an arrangement was at most a breach of a relatively minor provision of the HUD contract,<sup>171</sup> the court upheld the § 371 conviction.<sup>172</sup> It found that there was “a fundamental compromise of . . . HUD's[] interest in having its projects ‘administered honestly and officially and without corruption and waste.’”<sup>173</sup> Whereas the agency in *Gallup* suffered harm to a general interest, off-label promotion harms the FDA's specific interest in maintaining its approval process, making “fundamental compromises” of that process by drug manufacturers an even more serious offense.<sup>174</sup>

*Gallup* allows for a forthright application of the regulated benefits formulation in part because its facts lack instances of overt misrepresentation. But other cases whose holdings rely on evidence of misrepresentation have at least emphasized this principle in dicta. In *Barker Steel Co.*, the First Circuit held that misrepresentations made to general contractors constituted acts in furtherance of a conspiracy to defraud the Minority Business Enterprise (MBE) programs of the Department of Transportation and the Environmental Protection Agency.<sup>175</sup> The Barker Steel Co. operatives intentionally caused the general contractors to misrepresent that Barker Steel Co. was a minority-owned business, which enabled them to secure federal contracts not intended for them.<sup>176</sup> The court employed the specter of “affirmative acts of misrepresentation and deceit” to distinguish its holding from the Fifth

170. *Gallup*, 812 F.2d at 1278.

171. *Id.* at 1273 (“One provision in the contract prohibited the PHA from entering into any contract or property project in which any officer, employee or board member has any interest . . .”).

172. *Id.* at 1280.

173. *Id.* at 1276 (quoting *United States v. Conover*, 772 F.2d 765, 771 (11th Cir. 1985), *aff'd in part sub nom. Tanner v. United States*, 483 U.S. 107 (1987)).

174. *See Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 70 (D.D.C. 1998) (recognizing that the FDA has a substantial interest in forcing off-label uses through the on-label approval process), *vacated in part sub nom. Wash. Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000).

175. *United States v. Barker Steel Co.*, 985 F.2d 1123, 1135 (1st Cir. 1993) (holding that a § 371 allegation must at least establish that “[defendants] conspired to cause [a third party] to make misrepresentations to [a federal agency]” (citing *Tanner v. United States*, 483 U.S. 107, 132 (1987))).

176. *Id.* at 1126.

Circuit's decision to overturn a § 371 conviction in *United States v. Porter*.<sup>177</sup> But the court concluded by announcing: "In other words, the defendants had a duty imposed pursuant to § 371 not to divert the benefit of the MBE programs from their intended recipients . . . to themselves."<sup>178</sup> Rather than save this pronouncement as a dictum in its conclusion, the court should have used it as a basis for distinguishing *Porter*. After all, the *Porter* court held that those defendants were not under a duty to choose the course of action preferred—but not mandated—by the government.<sup>179</sup>

A *Barker Steel Co.* rubric founded on misrepresentation cannot be applied to all acts of off-label marketing any more than the *Klein* rubric, but one founded on the idea of regulated benefits can. We can generalize from this principle in a way that takes into account the interrelatedness of two distinct types of injuries: competitive injuries suffered by third parties and nonpecuniary injuries suffered by the government. Stated formally: even absent misrepresentations, a defendant may still defraud the United States when (1) it undermines a legitimate government function or objective (2) by securing for itself those benefits<sup>180</sup> (3) intended solely for another.<sup>181</sup> As applied: a drug manufacturer, even when engaged in truthful marketing, may defraud the United States if, in promoting a drug for unapproved uses, it secures for itself those benefits of the new drug approval process intended solely for those who have complied with the regulatory scheme.

The usurpation of a regulated benefit goes to the core of frustrating the FDA's mission because it makes it inefficient for competitors to undertake the costly process of securing a supplemental new drug application (SNDA) when they could instead promote their drugs off-label. Of course, there will be a question of fact, in the case of truthful off-label promotion, as to whether the promoter really does secure for itself the regulated benefits of another. In cases of direct-to-consumer advertisement, for example, there is a clear usurpation of regulated benefits. But even the ability of a company's representatives to make claims about developments in scientific evidence is treated as a regulated benefit of FDA approval.

---

177. *Id.* at 1130–31 (citing *United States v. Porter*, 591 F.2d 1048 (5th Cir. 1979)).

178. *Id.* at 1136.

179. *See Porter*, 591 F.2d at 1054–56 (overturning a § 371 conviction where the defendant did not violate any Medicare rules, regulations, or requirements by using a manual lab with which he could split reimbursement instead of an automated lab with which he could not).

180. *Cf. Barker Steel Co.*, 985 F.2d at 1134 ("The defendants' actions, as alleged, involved deceit and trickery to benefit the defendants by hampering a lawful government function.").

181. *Cf. id.* at 1132 ("The result was that a non-MBE got the benefit of contracts which the MBE program intended for minority businesses.").

Competitors assert this legal conclusion, in another context, when they bring unfair competition suits under section 43(a) of the Lanham Act.<sup>182</sup> Although section 43(a) cannot serve as a private right of action for violation of FDA regulations, the standard for what constitute “false or misleading”<sup>183</sup> competitive claims reinforces the idea of FDA supremacy. Even the government recognizes that the threat posed by such a suit serves as an indirect means of FDA enforcement.<sup>184</sup> In the case of *Zeneca Inc. v. Eli Lilly & Co.*,<sup>185</sup> the maker of a drug approved for reducing the risk of breast cancer brought a Lanham Act suit against the maker of a drug approved for postmenopausal osteoporosis on the grounds that the defendant was promoting its drug as effective in reducing the risk of breast cancer.<sup>186</sup> The court’s decision is significant in two respects: it recognizes that off-label promotion “hurt[s] competitors who are marketing a drug that has been established” as appropriate for the use being promoted,<sup>187</sup> and it establishes the FDA’s de facto authority in concluding that off-label claims are false.<sup>188</sup>

A Lanham Act plaintiff can satisfy its burden of proving the literal falsity of off-label claims by demonstrating that the tests relied on by the promoter “are not sufficiently reliable to permit one to conclude . . . that they established the claim made.”<sup>189</sup> On the question of whether the tests were sufficiently reliable, the *Zeneca* court found that the “FDA’s conclusion *as reflected in the [drug’s] label* and various FDA documents . . . is persuasive evidence that [the defendant’s] claims to the

182. 15 U.S.C. § 1125(a) (2006); *see also* HUTT ET AL., *supra* note 97, at 478 (describing the private unfair competition right of action created by the Lanham Act).

183. 15 U.S.C. § 1125(a).

184. Government prosecutors have, in the past, explicitly encouraged private enforcement by pharmaceutical companies. For example, a First Assistant U.S. Attorney for the District of Massachusetts once publicly encouraged companies to bring off-label suits against their competitors in order to protect their lawfully gained labels. Paul Greenberg & Tamar Sisitsky, *Off-Label Marketing Investigations in the Pharmaceutical Industry*, ANALYSIS GROUP F., Fall/Winter 2006, at 3, 4, *available at* [http://analysisgroup.com/uploadedFiles/Publishing/Articles/Forum\\_Fall06\\_Off-Label\\_Investigations.pdf](http://analysisgroup.com/uploadedFiles/Publishing/Articles/Forum_Fall06_Off-Label_Investigations.pdf); *see also* HUTT ET AL., *supra* note 97, at 478 (discussing the Lanham Act briefly as one optional avenue for parties to contest their competitors’ product claims).

185. *Zeneca Inc. v. Eli Lilly & Co.*, No. 99 CIV. 1452(JKG), 1999 WL 509471 (S.D.N.Y. July 19, 1999).

186. *See id.* at \*1.

187. *Id.*

188. *See id.* at \*33–34.

189. *Id.* at \*31 (quoting *McNeil-P.C.C., Inc. v. Bristol-Myers Squibb Co.*, 938 F.2d 1544, 1549 (2d Cir. 1991)) (internal quotation marks omitted).

contrary are untrue.”<sup>190</sup> In that case, the false claims were made both in an absolute sense—that the drug was effective in reducing the risk of cancer—and in a relative sense—that the drug was superior or comparable to its competitor’s drug, which *was* approved for that use.<sup>191</sup> The inescapable conclusion is that the FDA holds itself out as the only institutional route through which investigative studies may be conducted if one aim of those studies is to market a drug for an unapproved use. Those who have conducted their studies under FDA guidance and supervision benefit from making certain off-label claims. Those who circumvent this scheme diminish the incentive the FDA offers those who wish to enjoy its regulated benefits.

But where there is evidence of truthful off-label promotion by sales representatives to practicing physicians, and there truly is sufficient scientific evidence to preclude a finding of actual falsity, the fact finder in a § 371 prosecution should be allowed to conclude that the manufacturer did not secure for itself a benefit intended solely for another. The FDA regulates drug labeling and advertisement, but it does not regulate physician’s prescribing practices.<sup>192</sup> Therefore, a discussion of recognized therapeutic value does not interfere with an FDA function—the most general formulation of the defraud offense. And in any event, the agency may still protect its interests by bringing a number of other enforcement actions against the manufacturer, including misdemeanor charges under 21 U.S.C. § 333(a)(1).

The foregoing discussion of regulated benefits should not be confused with the question of whether each conspirator expects to benefit from a purported conspiracy to defraud the United States. In *Gallup*, the court concluded that “benefit, or a ‘stake in the venture’ is not an element of § 371.”<sup>193</sup> *Benefit* in that case referred not to the benefit gained by one who participates in a federal scheme, but rather the benefit that might or might not be gained by each individual conspirator—a pharmaceutical company or the sales agencies with which it contracts—as a result of participating in the conspiracy.

No single formulation of the defraud clause will provide guidance in prosecuting all the conduct envisioned by *Hammerschmidt* as falling within the scope the statute, but the benefits formulation offers the best

---

190. *Id.* at \*34 (emphasis added).

191. *Id.* at \*9.

192. 21 U.S.C. § 396 (2006) (“Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship.”).

193. *United States v. Gallup*, 812 F.2d 1271, 1278 (10th Cir. 1987) (quoting *United States v. Shoup*, 608 F.2d 950, 957 (3d Cir. 1979)).

guidance in cases of off-label promotion. The significance of devising an elegant formulation extends beyond the technicalities of criminal pleading. Choosing the correct formulation allows both government and industry to more accurately evaluate the legal significance of the conduct at issue. Doing so will lead to both clarity in marketing practices and accuracy in the calculation of the monies disgorged.

In the end, the institutional theory of off-label promotion is not at all novel. Although it does little to rationalize the substantive concerns that animate the FD&C Act's prohibitions section, it speaks to a broader governmental interest in the rule of law. But this interest works equally against prosecutor and defendant, just as it should benefit equally both the regulator and the regulated. The obvious advantage of having § 371 lie at the heart of prosecutions for regulatory crimes is that, however obscure the text of that statute might be, there remains a source upon which to build an intelligible doctrinal framework. The law should not shy away from defining an offense for fear of undercutting its deterrent effect. The institutional theory of off-label promotion plays an important role in ensuring the efficacy of government, but its reach should extend only so far as it can be neatly and concretely articulated.

#### V. CONCLUSION

If either theory presented in this Article is sufficient on its own to sustain an enforcement action against any of the pharmaceutical manufacturers, why care about carefully defining either one? The hope is that each might offer something unique to industry and regulators alike. The informational theory could offer a better understanding of where conflicts might arise in the field, thus allowing pharmaceutical counsel to implement more effective compliance programs. Likewise, regulators can offer more nuanced guidance about what kinds of communication they find most troubling, while relaxing restrictions on legitimate scientific exchange. The institutional theory might provide counsel with another framework for defending against government claims. It might offer the government a framework for more articulately prosecuting those claims. Both theories inform the structuring of remedies for misbranding violations.

