The First Amendment and FDA Restrictions on Off-Label Uses: The Call for a New Approach

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I. INTRODUCTION

The Food and Drug Administration (FDA) currently prohibits drug and device manufacturers from promoting off-label uses of drugs and devices, even if the information is truthful.1 FDA’s authority in this regard dates back to the effective date of the Food, Drug and Cosmetic Act (FDCA), when Congress empowered FDA with authority to regulate prescription drug labels.2 The current regulations restrict dissemination of all off-label information when the “speaker” is a drug or device manufacturer. In addition, to date, courts have assumed that off-label speech uttered by manufacturers always is promotional and thus deserving of the lesser First Amendment protection afforded to commercial speech.

While the government claims that the intention of the off-label speech regulations is to protect the public health by preserving a system of medical product approval, this black-and-white or talismanic approach restricts the free flow of information necessary for individual patient care. A new approach is necessary to ensure advancement of both the public health and the care and treatment of individual patients. In addition to reviewing the history and development of the regulatory milieu for the dissemination of off-label usage information, this article explores whether a new and more engaged and nuanced approach is necessary to achieve the goal of both industry and governments — better patient outcomes.

Exploring questions relating to First Amendment freedom of expression, and what is protected speech, requires contextual analysis. Much like Albert Einstein’s Special Theory of Relativity, the frame of reference of the observer affects what and how things are observed, notwithstanding that there are invariable constants.

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1 See, e.g., 21 C.F.R 202.1(e)(4), which provides:
An advertisement for a prescription drug covered by a new-drug application approved pursuant to section 505 of the act after October 10, 1962 or section 512 of the act after August 1, 1969, or any approved supplement thereto, shall not recommend or suggest any use that is not in the labeling accepted in such approved new-drug application or supplement. The advertisement shall present information from labeling required, approved, or permitted in a new-drug … application … relating to each specific side effect and contraindication in such labeling that relates to the uses of the advertised drug dosage form(s) or shall otherwise conform to the provisions of paragraph (e)(3)(iii) of this section.

2 Federal Food, Drug and Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040 (1938). When the FDCA was enacted in 1938 it included, among other things, a requirement that drugs have adequate labeling for safe use.
independent from all frames of reference. Put another way, what is observed is relative to the observer. Einstein’s theory was revolutionary because it challenged, and then overthrew Newton’s concepts of absolutism. Einstein’s observation is pertinent to the instant discussion because whether particular speech enjoys full First Amendment protection depends on the perspective from and the context in which it is observed. Fixing speech, even commercial speech, to a talismanic set of rules is the equivalent to the discredited fixed Newtonian frame of reference.

II. HISTORY AND REGULATORY FRAMEWORK

Off-label speech restrictions originated with the passage of the FDCA, which required FDA approval of all new drugs before commercial distribution. This extensive process includes a provision requiring manufacturers to obtain FDA approval of product labeling before commercial distribution of drugs and devices. The labeling must set forth, among other things, the indications for use (or the approved or cleared uses) and approved patient populations. Any unapproved indication is referred to as “off-label.”

FDA’s authority to regulate off-label speech arises from these labeling regulations in conjunction with the FDCA provisions relating to “adulterated” or “misbranded” products. Specifically, under the FDCA it is illegal to directly or indirectly distribute a product in interstate commerce that is “adulterated” or “misbranded.” A drug or device is “misbranded” if its labeling is “false or misleading in any particular.” In addition, a drug is “adulterated” if its labeling includes information regarding a use that FDA has not approved or cleared, including an unapproved dosage or patient population. Any new or additional use for a drug or device with an existing approved use requires separate approval, because the initial approval or clearance only applies to the specific indication, not to the product itself.

FDA’s authority to regulate off-label speech also arises in the context of the FDCA requirements relating to advertising of prescription drugs and restricted medical devices. Under the FDCA, advertisements must contain the established name of the product, the formula of the product, and a “brief summary” of side effects, contraindications, and effectiveness information. Violation of the advertising rules also misbrands the product.

In light of the restrictions on distributing misbranded or adulterated drugs and devices, in general, a manufacturer can only speak about an indicated, or “on-label,” use for a product. Manufacturer off-label promotion is illegal and subjects a company to various statutory penalties.

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11 Id.
12 For enforcement and penalty provisions, see, e.g., 21 U.S.C. §§ 331, 332, 333, and 372 (2002). Section 401 of the Food and Drug Administration Modernization Act (FDAMA), codified at 21 U.S.C. §360aaa, set forth certain conditions creating a safe harbor for distribution of information relating to off-label uses. FDA’s implementing regulations were codified at 21 C.F.R. pt. 99. In a March 2000 Notice continued...
III. LABELING AND PROMOTIONAL LABELING

Information considered “off-label” can only be understood in the context of the broad definition of “labeling.” Labeling is not confined to information affixed to a product. Instead, labeling is defined as, “[a]ll labels and other written, printed, or graphic matter 1) upon any article or any of its containers or wrappers, or 2) accompanying such article,”13 “One article or thing is accompanied by another when it supplements or explains it.”14 This is a very broad definition and encompasses many forms of information, including “[b]rochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature and reprints, and similar pieces of printed, audio, or visual matter descriptive of a drug and references published (for example, the Physicians Desk Reference).”15 There also is a separate definition for “promotional labeling.” Promotional labeling is anything that has a relationship to the product that is not approved product labeling. Claims made in promotional labeling must be consistent with approved labeling.16

IV. IMPERMISSIBLE OFF-LABEL SPEECH—THE ASSUMPTION OF PROMOTION

It is important to note from the outset that speech regarding off-label usage of a medical product is not always illegal. Instead, off-label speech is regulated based on the identity of the speaker, the substance of the communication and the context of the speech. For example, while manufacturers are not permitted to speak about off-label usage, medical practitioners and the rest of the public are so permitted. This distinction is based on an assumption that a manufacturer’s intention for disseminating off-label information is always product promotion. However, such an assumption is not always warranted and excludes an analysis based on all of the factors above.

Off-label promotion has not been statutorily defined, but case law provides some guidance. According to the court in the initial Washington Legal Foundation case, off-label promotion is promotion of a drug for an indication, dosage and/or population that has not been approved by FDA and is therefore not listed on the

FDA clarified that dissemination of off-label materials falling outside of the safe harbor would not constitute a per se violation of law. 65 Fed. Reg. 14286 (March 16, 2000). This Notice, however, did not alter the power of laws prohibiting misbranding and adulteration. Indeed, 21 C.F.R. 99.405 provided that “[t]he dissemination of information relating to a new use for a drug or device may constitute labeling, evidence of a new intended use, adulteration, or misbranding of the drug or device if such dissemination fails to comply with section 551 of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. 360aaa) and the requirements of this part. A manufacturer’s failure to exercise due diligence in submitting the clinical studies that are necessary for the approval of a new use that is the subject of information disseminated under this part or in beginning or completing such clinical studies shall be deemed a failure to comply with section 551 of the act and the requirements of this part.” FDAMA Section 401 ceased to be effective on September 30, 2006 leaving manufacturers with no policy protecting distribution of off-label information.

approved product labeling. Various forms of communication regarding off-label usage have been dubbed “promotion.” For example, the following have all been considered promotion activities: certain company-supported scientific or educational activities that relate to a company’s products and include discussion of off-label uses; distribution of internally authored marketing materials to prescribers regarding off-label uses; initiation of person-to-person contact between sales representatives and prescribers regarding off-label uses; direct-to-consumer advertisements discussing off-label uses, including distribution of studies and abstracts regarding off-label uses without adhering to FDA requirements; and improper dissemination of information about an investigational drug during a clinical trial.

V. PERMISSIBLE OFF-LABEL SPEECH

As noted, while a manufacturer generally cannot speak in a promotional manner about an off-label use, it is legal for physicians to speak about and prescribe a product for an off-label purpose. This paradox creates the untenable result that a manufacturer is prohibited from informing physicians about any standard of care involving off-label use. In fact off-label use is a common medical practice in the United States and may be recognized as the standard of good medical care in many circumstances.

18. There is a fine line between promotion versus scientific dissemination of information when a company sponsors a Continuing Medical Education (CME) during which off-label use of its drug is discussed. Physicians are permitted to discuss off-label uses of a drug, but perception of company influence over the physician may lead to the conclusion that the discussion is promotional and not scientific.
21. For example, 21 C.F.R § 312.7(a) provides, A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.
22. In fact, 21 U.S.C. § 396 expressly states, “[n]othing in this chapter shall be construed to limit or interfere with the authority of a healthcare practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease....” In addition, the Supreme Court in Buckman v. Plaintiffs’ Steering Committee, 531 U.S. 341, 350 (2001), stated that off-label use of FDA-regulated products is an “accepted and necessary corollary” to FDA’s regulatory scheme.
23. According to a 2006 study, slightly more than 20 percent of all prescriptions written in physician offices were off-label, and approximately 46 percent of prescriptions for cardiovascular purposes were off-label. See David C. Radley et al., Off-label Prescribing among Office-Based Physicians, 166 ARCH. INTERN. MED. 1021, 1023 (2006).
24. See WLF II at 56-57 (citing acknowledgement by FDA that off-label uses may benefit public health in certain circumstances). FDA most recently recognized that off-label use of medical products continued
The dichotomy between an explicit recognition that off-label use may be the standard of appropriate medical care and an absolute prohibition of manufacturer off-label speech on the very same subject reveals the differing perspectives and objectives of practicing physicians and FDA. For the practicing physician, the primary objective is the care and treatment of each individual patient, while, by statute, FDA is charged with the protection of the public health.25

While the intent of the FDCA is to protect and advance public health, considerations of individual health and welfare need not be disregarded during creation of policies aimed at protection of the larger population. Unintended adverse consequences for individuals or a smaller population should be considered before implementation of any law or regulation aimed toward the greater public. There are ways to harmonize better the goals of protecting the public health and an individual’s health. Flexible rather than strict enforcement is a more ethical approach to protecting the public. Off-label dissemination policies should be guided by recognition that different actors (e.g., physicians and regulators) are working in different contexts and with different perspectives, yet both seeking to achieve the same goal—improvements in human health and welfare.

VI. ENFORCEMENT AUTHORITY

FDA enforces off-label promotion rules through Warning Letters, Untitled Letters, civil actions, injunctive relief and criminal actions.26 FDA has used these tools, including the imposition of criminal penalties, on numerous occasions over the past several years. For example, Orphan Medical, Inc. recently pleaded guilty to charges that it intentionally misbranded the drug Xyrem by marketing the drug for off-label purposes.27 A psychiatrist and Orphan Medical sales representative were also separately charged with the same allegations.28 The company agreed to pay a $5 million fine and more than $12 million in restitution. In October 2006, InterMune, Inc. agreed to pay $36.9 million to resolve allegations that it violated the federal Civil False Claims Act by knowingly causing the submission of claims that were not eligible for reimbursement because they were for unnecessary and/or off-label uses of its drug Actimmune.29 In May 2004, Warner-Lambert pleaded guilty may constitute a standard of care. See Draft Guidance. FDA stated, “These off-label uses or treatment regimens may be important and may even constitute a medically recognized standard of care. Accordingly, the public health may be advanced by healthcare professionals’ receipt of medical journal articles and medical or scientific reference publications on unapproved or new uses of approved or cleared medical products that are truthful and not misleading.” Id. at 2.

29 Press Release, U.S. Department of Justice, Biopharmaceutical Company InterMune, Inc. to Pay Nearly $37 Million for Unlawful Marketing of Actimmune (Oct. 26, 2006), available at http://www.usdoj.gov/usa/cen/press/2006/2006_10_26_InterMune.Deferred.prosecution.agreement.press.html. Although Actimmune was approved by FDA for the treatment of chronic granulomatous disease and severe, malignant osteopetrosis, the vast majority of sales of the drug between August 2002 and January 2003 resulted from prescriptions for the treatment of IPF, a debilitating fatal lung disease even though Phase III clinical trials of the drug from 2000 to 2002 failed to establish statistically significant evidence of benefit for use in IPF. The InterMune press release discussing the clinical trial results (which in the government’s view was misleading), which discussed the use of Actimmune for IPF was distributed to pulmonologists and Actimmune® patients. In addition, the government alleged that, notwithstanding the clinical trial results, InterMune’s sales personnel were encouraged to (and did) inform physicians of a claimed survival benefit in mild to moderate IPF patient populations and allegedly distributed, or showed, the press release to physicians during sales visits.
to charges of promoting Neurontin for unapproved uses in violation of 21 U.S.C. §§ 331(a), 331(d), 333(a), 352(f)(1) and 355. These examples are a few among the number of circumstances where FDA recently used available enforcement tools in the context of off-label promotion. The stakes for companies clearly are high.

**VII. INDIVIDUAL PATIENT CARE**

While the stakes clearly are high from a company’s perspective, the stakes are also high from a patient care perspective. The penalties and risks associated with enforcement action stifle off-label related speech even when the listener may require the information in order to meet standard professional requirements relating to care of individual patients. Where off-label use of a drug is the accepted standard of care, which is often the case for pediatric and cancer patients, physicians would benefit from receiving information regarding off-label use in a timely manner, especially information indicating that the off-label use may not be safe or effective in particular doses or for particular populations, as well as information obtained by the company regarding positive patient outcomes associated with the off-label use.

In its recently published draft guidance on reprint and distribution off-label materials, FDA recognizes that off-label usage of a medical product may represent the standard of care for treatment by a physician. Consequently FDA recognizes that a physician may fail in his or her responsibilities to a patient if off-label use is not considered or attempted in treatment. Yet, FDA’s policy, as stated in the Draft Guidance, continues to impede a practitioner’s ability to carry out this responsibility, focusing on a broad view of public health over individual patient health.

**VIII. FIRST AMENDMENT ANALYSIS**

Congress empowered FDA with authority to regulate drug labeling and advertising and thereby restrict off-label speech before the First Amendment implications of “commercial speech” were brought before the courts. Since then, several courts have been called on to analyze the constitutionality of FDA off-label speech restrictions in various contexts. To date, First Amendment analysis of off-label speech restrictions has been performed under the commercial speech doctrine set

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32 Draft Guidance.

33 The Draft Guidance addresses the types of reprints, articles and reference publications that may be distributed by manufacturers and the manner in which the information should be disseminated. It dispenses with the more onerous criteria set forth in the FDAMA safe harbor such as commitment to submit a supplemental application for the new use within six months of dissemination. In fact, the Draft Guidance specifically provides, “Given the sunset of FDAMA § 401, the other elements that comprised § 401 which are not specifically described in this draft guidance are no longer applicable.” Draft Guidance at 2.

34 The concept of commercial speech in this context was defined in Virginia State Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc., as speech that does not more than “propose a commercial transaction.” 425 U.S. 748, 762 (1976). This definition was expanded in the *Central Hudson* case to include any “expression related solely to the economic interests of the speaker and its audience.” Central Hudson Gas & Electric. Corp. v. Public Service Comm’n of New York, 447 U.S. 557 (1980).
forth in *Central Hudson Gas & Electric Corp. v. Public Service Commission of New York.*[^35] A broad assumption that *all* off-label speech uttered by a manufacturer is “commercial” and therefore deserving of the lower First Amendment protection afforded to commercial speech, by design, restrains the free flow of fully protected scientific speech and has a chilling effect on distribution of information that would benefit public health in the aggregate.

**IX. Off-Label Information is Scientific Speech**

The *WLF II* court recognized that the type of speech the FDA off-label regulations restricts is not actually, in many cases, the manufacturer’s own speech.[^36] Most often, the off-label information takes the form of scientific journal articles, medical case studies and continuing medical education course enduring materials.[^37] The underlying speech, therefore, is fully protected scientific speech. Indeed, unless a manufacturer is the speaker, the speech is entirely legal and fully protected.

Scientific speech has been grouped with “literary and artistic speech” as deserving of the highest level of First Amendment protection.[^38] In *WLF II* the court saw as “beyond dispute” that all scientific articles, books, or symposium presentations by non-manufacturer speakers about off-label prescription drug uses are “scientific and academic speech” meriting “the highest degree of constitutional protection.”[^39] Arguably, off-label speech, which often takes the form of scientific journal articles and academic presentations, should be considered scientific speech, even when uttered by manufacturers.[^40]

**X. Manufacturer Off-Label Speech is Considered Commercial**

There is no bright line definition of “commercial speech,” but one thing is clear — commercial speech does not receive full First Amendment protection. Since commercial speech was first recognized as a form of speech deserving a lower

[^35]: *Central Hudson*, 447 U.S. at 561.
[^36]: *WLF II* at 63.
[^37]: *Id.*
[^38]: See *Miller v. California*, 413 U.S. 15, 34 (1973) ("The First Amendment protects works which, taken as a whole, have serious literary, artistic, political, or scientific value…."); *Roth v. United States*, 354 U.S. 476, 484 (1957) (stating that the First Amendment embraces "[a]ll ideas having even the slightest redeeming social importance," including the "advancement of truth, science, morality, and arts in general" (quoting 1 JOURNALS OF THE CONTINENTAL CONGRESS 108 (1774))); Bd. of *Trs. of Leland Stanford Junior Univ. v. Sullivan*, 773 F. Supp. 472, 474 (D.D.C. 1991) ("It is…settled…that the First Amendment protects scientific expression and debate just as it protects political and artistic expression."). Very few cases have defined “scientific” in the context of the First Amendment protection. See *Sullivan*, 773 F. Supp. at 474 (stating that the First Amendment status of scientific expression and debate is less commonly litigated), cited in *WLF*, 13 F. Supp. 2d at 62.
[^40]: In other contexts, scientific speech having at least one commercial purpose retains full First Amendment protection. For example, scientific speech is fully protected even if the speaker touts one product over another. *See Gordon & Breach Science Publishers v. American Institute of Physics*, 859 F. Supp. 1521, 1539 (1994) (noting “product-specific scientific articles should be seen as they appear to the world — as expressions of disinterested academic inquiry”); *see also* Oxycal Lab., Inc. v. *Jeffers*, 909 F. Supp. 719, 725 (S.D. Cal. 1995) (holding that minimal reference to a commercial product throughout a longer does not establish central message as commercial, the book retains full protection as a literary work).
level of First Amendment protection, it has been defined with varying degrees of vagueness. For example, at one time, the Court defined “commercial speech” in terms of “common sense,” essentially using the “you know it when you see it” approach. Quoting Ohralik and Virginia State Bd. Of Pharmacy, the Court stated that the, “commercial speech doctrine rests heavily on ‘the “common-sense” distinction’ between speech proposing a commercial transaction…and other varieties of speech.”

Another vague definition of commercial speech was presented before the commercial speech doctrine was officially recognized, but carried through into later commercial speech decisions. In Pittsburgh Press Co. v. Pittsburgh Commission on Human Relations Comm., the Court stated that commercial speech is speech that does “no more than propose a commercial transaction.” Adding to the confusion another definition was presented in 1980 when the Central Hudson Court defined commercial speech as, “expression related solely to the economic interests of the speaker and its audience.” Given these broad and vague definitions, the Court has struggled to apply the commercial speech doctrine in consistent manner. These definitions leave the door wide open for the unwarranted designation of all manufacturer speech as commercial.

Despite these definitional difficulties, the Court’s approach does take into consideration the fine distinctions and the case specific nature of the inquiry into the nature of the speech. If the regulatory goal limiting commercial speech is to protect an unwary public from sharp commercial practices, then the relative understanding of the subject matter by the listener must be considered in order to determine if the practices are misleading. This is precisely what courts need to be doing when

41 For a comprehensive analysis of the history of various definitions of “commercial speech” since the inception of the doctrine, see Glenn C. Smith, Avoiding Awkward Alchemy—In the Off-label drug context and beyond: Fully-Protected Independent Research Should Not Transmogrify into Mere Commercial Speech Just Because Product Manufacturers Distribute It,” 34 WAKE FOREST L. REV. 963 (Winter 1999).

42 Zauderer v. Office of Disciplinary Counsel, 471 U.S. 626, 637 (1985) (quoting Ohralik v. Ohio State Bar Ass’n, 436 U.S. 447, 455-56 and Virginia State Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc., 425 U.S. 748, 772 (1976)) (emphasis added) (“[m]ore subject to doubt, perhaps, are the precise bounds of the category of expression that may be termed commercial speech, but it is clear enough that the speech at issue in this case—advertising pure and simple—falls within those bounds.”) See, e.g., Rubin v. Coors Brewing Co., 514 U.S. 476, 493-494 (1995) (Stevens, J., concurring) (“As a matter of common sense, any description of commercial speech that is intended to identify the category of speech entitled to less First Amendment protection should relate to the reasons for permitting broader regulation: namely, commercial speech’s potential to mislead.”); Edenfield v. Fane, 507 U.S. 761, 765 (1993) (“Ambiguities may exist at the margins of the category of commercial speech…”); Bolger, 463 U.S. at 82 (Stevens, J., concurring) (“The impression that ‘commercial speech’ is a fairly definite category of communication … may not be wholly warranted.”). The 1976 case that originated the “common sense” phrase used a revealingly tepid back-handed phrase in describing the commercial/non-commercial distinction: “In concluding that commercial speech enjoys First Amendment protection, we have not held that it is wholly undifferentiable from other forms.” Virginia State Bd., 425 U.S. at 772 n.24.


44 Central Hudson, 447 U.S. at 561.

45 See, e.g., Central Hudson, 447 U.S. at 579-80 (Stevens, J., for himself and Brennan, J., concurring). Justice Stevens elaborated:

Neither a labor leader’s exhortation to strike, nor an economist’s dissertation on the money supply, should receive any lesser protection because the subject matter concerns only the economic interests of the audience. Nor should the economic motivation of a speaker qualify his constitutional protection; even Shakespeare may have been motivated by the prospect of pecuniary reward. Thus, the Court’s first definition of commercial speech is unquestionably too broad.
assessing speech, namely, taking into account the relative knowledge, sophistication and perspectives of the parties and their motivations. In the case of peer reviewed scientific articles sent to healthcare professionals, the analysis is very different than if the same information was sent to the general public.

The risk of mislabeling non-commercial speech as “commercial” rests on the fact that “commercial speech” is afforded a lower level of First Amendment protection. It is well-settled that “the First Amendment…protects commercial speech from unwarranted governmental regulation.”46 “If commercial speech only is threatened, however, the requirements of the First Amendment are less rigorous.”47 Accordingly, courts have protected commercial speech, but have limited protection to “the dissemination of truthful and non-misleading commercial messages about lawful products and services.”48

XI. HYBRID SPEECH

Recognizing that some speech may be mixed commercial and non-commercial, in the 1983 decision of Bolger v. Youngs Drug Products Corp., Justice Marshall provided a three-prong test for characterizing speech that does not fit neatly into what he called the “core notion of commercial speech.”49 Bolger involved a case of what the Court referred to as “hybrid speech.”

The Court was tasked with defining the constitutional protection of informational pamphlets distributed by a contraceptive manufacturer. While the pamphlets contained “discussions of important public issues such as venereal disease and family planning,” they also included references to the particular contraceptive brand the manufacturer sold. In deciding that the pamphlets were commercial speech, the Bolger majority relied on “the combination of all” these factors: 1) that the pamphlets were conceded to be advertisements, 2) that they “referenced a specific product,” and 3) that the pamphlet distributor had “an economic motivation for mailing the pamphlets.” The Court stated that none of the three factors alone was dispositive, but the presence of all three factors “provides strong support” for a finding that the speech is commercial. “The key seems to be a determination of whether the speech is primarily motivated by commercial concerns, or whether there are sufficient non-commercial motivations.”50

The Bolger decision emphasizes an analysis that is often overlooked, specifically, that it is the motivation for the speech that becomes the focal point of the evaluation and may, in itself, be dispositive. For instance, if a company disseminates a peer reviewed article warning about risks associated with certain off-label uses in order to minimize adverse outcomes, the speech should not be considered commercial in nature. From a different perspective, however, the same speech could be viewed as commercial because the dissemination seeks to reduce potential liability. Merely seeking to avoid liability based upon a use that is not approved, cleared or promoted, on the other hand, seems to be a far cry from promotional activity seeking to increase company revenues.

46 Valley Broadcasting Co. v. United States, 107 F.3d 1328, 1330 (9th Cir. 1997) (“restrictions that might be inconsistent with the First Amendment’s protection of other varieties of speech are tolerated in the area of commercial speech”).
47 Id.; Central Hudson, 447 U.S. at 562 n. 5.
50 Oxycal Labs., 909 F. Supp. at 725.
The point is that the identification of the type of speech involved in every off-label communication should not be reached simply because of the actor who is speaking. Rather, the facts of the situation, including content, context and motivation should all carefully be analyzed before coming to any conclusion. Following Bogler, some courts have analyzed off-label information disseminated by a manufacturer as hybrid speech.51 The WLF II court recognized that such off-label speech, “is the speech of others—the work product or scientists, physicians and other academics.”52 In the end, however, these courts have shied away from this intentional analysis and have determined that manufacturer off-label speech is per se “commercial,” deserving of lower First Amendment protection, based simply on the manufacturer as the speaker. Even so, the analysis of the restrictions on manufacturer “commercial” speech under the often-cited Central Hudson doctrine has itself raised serious constitutional questions regarding the power of the agency to regulate truthful, non-misleading speech.

XII. OFF-LABEL PROMOTIONAL ACTIVITY IS SPEECH

As a threshold matter, for the First Amendment to apply, the restricted activity must be speech rather than conduct. The courts that have considered the constitutionality of off-label promotion restrictions have proceeded on the basis that dissemination of off-label information is speech, not conduct. For example, the court in WLF II, stated, “this court is hard pressed to believe that the agency is seriously contending that ‘promotion’ of an activity is conduct and not speech, or that ‘promotion’ is entitled to no First Amendment protection.”53

XIII. OFF-LABEL PROMOTIONAL SPEECH IS CONSIDERED COMMERCIAL

As noted, the few cases which have addressed whether FDA can restrict off-label speech have concluded that off-label promotion is commercial speech.54 The analysis of whether off-label speech is commercial should turn on the totality of the circumstances surrounding the speech.55 A totality of the circumstances approach would require a more case-by-case analysis. As written, however, the off-label speech regulations restrict a manufacturer’s ability to disseminate all off-label information.

As set forth below, the assumption that all off-label speech is commercial is not always correct. By way of background, however, the following sets forth the analysis that courts presently use to analyze the constitutionality of FDA’s off-label speech regulations.

XIV. CENTRAL HUDSON AND OFF-LABEL SPEECH RESTRICTIONS

To determine whether FDA’s limitations on off-label speech are constitutional under the First Amendment commercial speech doctrine, courts apply the four-pronged Central Hudson test asking whether: 1) the speech concerns lawful activ-

51 WLF II at 62 (quoting Bogler, 463 U.S. at 81 (Stevens, J. concurring)).
52 Id
53 WLF II
55 Bolger, 463 U.S. at 66-6. The commercial speech doctrine was first recognized in the 1976 Supreme Court case, Virginia State Bd., 425 U.S. at 770 when the Court concluded “that commercial speech, like other varieties, is protected.”
ity and is not misleading; 2) the asserted government interest is substantial; 3) the regulation directly advances the substantial governmental interest; and 4) the regulation is not more extensive than necessary to serve that interest.\footnote{Central Hudson, 447 U.S. at 566.}

If paternalism or mistrust of how the public will use the information is the basis of the restriction, courts generally strike it down.\footnote{44 Liquormart, 517 U.S. at 517 (Scalia, I, concurring).} “[A] State’s paternalistic assumption that the public will use truthful, non-misleading commercial information unwisely cannot justify a decision to suppress it.”\footnote{Id.} For example, in \textit{Western States} the Supreme Court rejected the notion that the Government has an interest in preventing the dissemination of truthful commercial information in order to prevent members of the public from making bad decisions with the information.\footnote{Western States, 535 U.S. at 374.} In fact, at least one Justice of the Court finds that paternalism is a \textit{per se} illegitimate reason for restricting commercial speech.\footnote{Greater New Orleans Broad. Ass’n v. United States, 527 U.S. 173, 197 (U.S. 1999) (Justice Thomas, concurring in the judgment) (citing 44 Liquormart, 517 U.S. at 484) (“I continue to adhere to my view that ‘in cases such as this, in which the government’s asserted interest is to keep legal users of a product or service ignorant in order to manipulate their choices in the marketplace,’ the \textit{Central Hudson} test should not be applied because ‘such an ‘interest’ is \textit{per se} illegitimate and can no more justify regulation of ‘commercial speech’ than it can justify regulation of ‘noncommercial’ speech’.”).} The rule disfavoring a paternalistic approach is particularly true where the recipient of information is a sophisticated listener trained extensively in the use of such information, such as a physician making prescribing decisions.\footnote{See Washington Legal Foundation v. Henney, 56 F. Supp. 2d 81, 86 (D.D.C. 1999) [hereinafter WLF III].}

\textbf{XV. IS SPEECH LAWFUL AND NOT MISLEADING?}

Under Prong One of \textit{Central Hudson}, the court must determine that the speech is not false or misleading and the conduct underlying the subject of the speech is not illegal. Courts have drawn a distinction between the concept of “false and misleading” in the FDCA misbranding regulations and the concept of “false and misleading” under Prong One of the \textit{Central Hudson} test. The misbranding provisions of the FDCA prohibit a manufacturer from making false or misleading statements about its product. Under these provisions, FDA would consider truthful information regarding off-label use “false and misleading” because it is not an approved or cleared use. Courts have held, however, that the mere fact that speech would be considered false and misleading under the FDCA does not automatically make it false or misleading under Prong One of \textit{Central Hudson}. If the information about the drug’s use is truthful, even though the use is not indicated on the label, it is not false under the \textit{Central Hudson} test. With regard to legality, because it is legal for physicians to use a drug for off-label purpose (the conduct underlying off-label speech), courts have found that truthful speech about off-label use is not illegal.\footnote{See WLF II, Caputo, 288 F. Supp.2d at, 920-21.}

\textbf{XVI. IS THE GOVERNMENT INTEREST ADVANCED SUBSTANTIAL?}

Under Prong Two of \textit{Central Hudson}, any speech restriction must be related to a legitimate government interest.\footnote{Central Hudson, 447 U.S. at 564-565.} Cases that have addressed Prong Two in the
area of FDA-regulated speech generally have identified two potential government interests: 1) protecting public health; and 2) encouraging submissions of new drug indications to FDA for approval.64

With regard to the public health interest, FDA argues that promoting unapproved uses can lead to dangerous uses of drugs.65 With regard to encouraging submissions of new indications to FDA approval, FDA argues that permitting off-label promotion is a disincentive for obtaining FDA approval for the off-label indication.66 In *Western States*, the Court stated, “preserving the effectiveness and integrity of the FDCA’s new drug approval process is clearly an important government interest, and the government has every reason to want as many drugs as possible to be subject to that approval process.”67

XVII. DOES THE REGULATION DIRECTLY ADVANCE THAT INTEREST?

Prong Three of *Central Hudson* requires that the speech restriction effectively advance the government interest identified in Prong Two. In *WLF III* and *WLF II*, the court rejected the idea that a restriction on dissemination of scientific articles and medical text books relating to off-label uses directly advances public health.68 The court did, however, find that the speech restriction effectively advanced the interest of ensuring that manufacturers seek approval for off-label uses. The court stated that, “[o]ne of the few mechanisms available to FDA to compel manufacturers to seek approval for off-label uses is “to constrain their marketing options; i.e. control the labeling, advertising and marketing.”69 Accordingly, courts have consistently found that at least one substantial government interest is advanced by restricting off-label speech.

XVIII. IS THE REGULATION MORE EXTENSIVE THAN NECESSARY?

Prong Four of *Central Hudson* requires that the restrictions on speech be the least burdensome approach to accomplish the government interest. Courts have used Prong Four to invalidate FDA speech restrictions in cases such as *Western States* and *WLF*. Those cases, however, only addressed the specific speech restrictions at issue. For example, *Western States* addressed advertisement of pharmacy compounding services and the *WLF* cases involved peer-reviewed medical and scientific articles and books and off-label discussions held during CMEs. While the court in *WLF* enjoined FDA from prohibiting dissemination of enduring materials (scientific articles, text books, etc.) and communication regarding off-label use during CMEs, the court made a point to note that other mechanisms to meet the government interest were still available.

The fact that these adequate incentives still exist to get off-label treatments on-label is central to this court’s finding that the First Amendment is violated by the Guidance Documents. Were manufacturers permitted to engage in all forms of marketing of off-label treatments, a different result might be compelled.70

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64 See, e.g., *WLF II* at 69.
65 See, e.g., Final Guidance at 64.079-80.
66 See, e.g., *Western States*, 535 U.S. at 368 (defining the government interest as ensuring the implementation of the FDA review and approval process).
67 *Western States*, 535 U.S. at 368-69.
68 *WLF III* at 86; *WLF II* at 70.
69 Id.
70 *WLF*, 13 F. Supp. at 73.
The fact-specific nature of these decisions was made clear in *Caputo* where the plaintiff sought to strike down as unconstitutional 21 C.F.R. § 801.4, the “apparent source of FDA’s authority to prohibit manufacturer promotion of off-label uses.”71 Under 21 C.F.R. § 801.4, if the “intended use” of a product changes, manufacturers are required to obtain FDA approval for the new use so that they can properly label the product with directions and other information regarding the new use. Rather than carving out methods that FDA might use to restrict off-label speech that would be burdensome (e.g., restriction on disseminating enduring materials), the court found that the general restriction was not more burdensome than necessary. Upholding the restriction, the court found that “permitting Defendants to engage in all forms of truthful, non-misleading promotion of off-label use would severely frustrate FDA’s ability to evaluate the effectiveness of off-label uses.”72 Tellingly, the court cited that section of the *WLF* decision where the court stated, “were manufactures permitted to engage in all forms of marketing of off-label treatment, a different result might be compelled.”73 Apparently, *Caputo* was just such case. Given the disagreement of the courts on this determination, the constitutionality of the current regulatory scheme and its fixed method of determining the type of speech based solely on the identity of the speaker, remains questionable.

**XIX. CURRENT OFF-LABEL REGULATIONS ARE TOO BROAD**

There is no question that the content of off-label speech in the form of peer reviewed medical literature is scientific.74 It only seemingly becomes commercial when distributed by a manufacturer. Some Justices have opined that even where commercial speech is at issue, “decisions that select among speakers conveying virtually identical messages are in serious tension with the principles undergirding the First Amendment.”75 Even if selection among speakers conveying the identical message passes constitutional muster, the assumption that manufacturer off-label speech is *always* “commercial” is misguided and arguably leads to unconstitutionally overbroad results.

Current off-label regulations and Guidances restrict *all* manufacturer off-label speech, regardless of whether the speech in fact advances a company’s economic interests, or by common sense, can be considered promotion or advertising. A keen example of when dissemination of off-label speech would not necessarily advance a company’s interests is where the article or case study reports a potential adverse event. Even if follow-up investigation later reveals that the adverse event was not related to the drug, timely dissemination of such information is crucial to public health.

In addition, the information would not meet the *Bolger* litmus test. Specifically, while the article or case study would likely reference a specific product, manufacturers would not concede that the information is advertising and there would not be an economic motivation for distribution. The motive would be public-health related. In fact, a failure to disseminate could result in tort law imposed sanctions, which

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72 *Id.*
73 *Caputo*, 288 F. Supp.2d at 922.
74 *WLF* II.
indicates that the government would also recognize the public health implications of manufacturer dissemination of off-label information relating to potential risks. Clearly, regulations that effectively undermine the asserted government interest are not narrowly tailored to meet that interest.

While the recently published Draft Guidance appears to be an attempt to balance public health with physicians’ need to care for patients on an individual basis, the Draft Guidance, like prior approaches, assumes that all distribution of scientific information is commercial speech subject to certain restrictions. It does not take into account the motivation for the communication that is noted in Bolger. For example, “Dear Doctor” letters clearly are not promotion. Yet, information disseminated in the types of articles addressed by the Draft Guidance could be exactly the type of information that would be disseminated in a “Dear Doctor” letter for an approved or cleared use. This situation is illogical and reveals the problem with viewing all manufacturer off-label speech as promotion. If the information that is being conveyed in the peer reviewed article mentioning the off-label use is of the same type that would give rise to a “Dear Doctor” letter for an approved use, the additional requirements set forth in the Draft Guidance should not be necessary. Similarly, the dissemination of peer reviewed information can also advance the treatment of disease and medical conditions. Recognizing that peer reviewed literature is the primary source of communicating medical observations and advancements and is in and of itself protected speech, the distributor of the article should not change the intrinsic nature of its content.

The critics of this Draft Guidance, principally Representative Henry Waxman, write that the Draft Guidance undercuts the essence of FDA regulation, because it creates a loophole that swallows the basic tenet of product approval and clearance. Representative Waxman argues that once a company has approval for a single use, the rest can be marketed off-label through scientific and medical literature distribution. Representative Waxman assumes that permitting off-label dissemination with conditions is a total abdication of FDA oversight responsibility. The fact that FDA is grappling with the issue reveals only that the current regulatory framework is not tailored to recognize both individual and public health—it does not portend FDA withdrawing from its gate keeping post. While it is true that manufacturers have an interest in more narrowly tailored off-label dissemination rules, there are other stakeholders—individual patients who benefit from unapproved uses of approved products, and physicians striving to provide the best care to their patients.

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To achieve the respective goals of individual patient care and public health protection there must be a conscious and active involvement of all stakeholders. The Draft Guidance is an attempt to permit manufacturer dissemination of very specific types of off-label information using a transparent approach to avoid regulatory approval through the use of peer reviewed reprints. FDA should be applauded for taking this first step, even though the Draft Guidance still falls short of validating the perspective of individual patients who benefit from off-label use of medical products and the physicians who care for them. An improved off-label regulatory scheme will discard a talismanic approach of “one size fits all,” and address unintended outcomes for individual patients.

XX. CONCLUSION

Despite numerous Guidances, rules, regulations, statutes and court decisions, a clear definition of what “speech” regarding off-label indications will subject drug and device manufacturers to FDA enforcement, including criminal charges, remains elusive. As written, the current regulations and Guidances restrict manufacturers from disseminating all off-label information. In light of the substantial statutory penalties imposed on manufacturers in the recent past, unless there is a significant change in approach, it is safe to say that a conservative approach to dissemination of off-label information is prudent. In light of the benefits of providing off-label information to physicians who are legally permitted to and do prescribe drugs and devices for off-label uses, First Amendment challenges to FDA’s various methods of restricting off-label speech will likely continue until definitive laws, regulations and approaches balancing the goals of individual patient care with the broader public health are codified and implemented.

The current approach of regulating speech based heavily upon the status of the communicator has not achieved the goal of protection of the public. Moreover, it has proven to be difficult in application and burdensome upon pharmaceutical and medical device manufacturers, medical professionals, FDA and the Department of Justice alike. The most effective approach that recognizes the interests of the public health and individual health, as well as the role of the skilled medical professional, would be to allow the distribution of peer reviewed medical literature to medical professionals which discuss off-label uses with a simple advisory that informs the physician of the following: 1) that the disseminated material discusses uses that are not approved or cleared by FDA; 2) that the physician should consider carefully all information about the product before using off-label; and 3) that the physician should exercise clinical judgment in consultation with the patient before using the product off-label.

Using this approach, the status of the communicator becomes irrelevant and the focus is placed where it belongs—on the informed decision of the medical professional in the context of the practitioner-patient relationship. First Amendment interests, public health concerns and individual care decisions are all respected with this approach which addresses many of the subtleties of this complex situation at the most basic level of care where it belongs. It also places liability in the proper context, namely, that the physician is responsible as a learned intermediary and the pharmaceutical or medical device manufacturer is responsible for the dissemination of truthful, balanced and non-misleading information. Finally, this approach would improve patient care in the off-label context by promoting transparent disclosure by
the medical device manufacturer and the health care provider so that the informed consent of the patient is truly informed. The time has come to regularize off-label use in a regulatory environment and the proposed approach effectively permits full information to the providers of healthcare and provides FDA with a means to monitor and enforce compliance.