

Addressing the Threshold: Regulating Off-Label Drug Promotion

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INTRODUCTION

The federal Food and Drug Administration (“FDA”) engages in a premarketing approval process established by Congress which permits the agency to restrict the sale of prescription drugs and approve medications for a specific purpose, typically the treatment of a specified medical condition or disease.¹ After a drug is approved for one specific purpose, medical professionals may discover other valuable uses for a particular drug—known as “off label uses”²—not formally approved by the FDA.³ For instance, where a drug has been approved by the FDA to treat chronic headaches, it has been approved for that one use only. An “off-label” use of that same drug refers to using the drug for an additional purpose unrelated to the FDA approved use of the drug, such as using the same drug to reduce cholesterol levels. In recognizing the value, and in some cases necessity of, prescribing off-label uses for certain medications, the FDA has traditionally given licensed medical professionals the discretion to prescribe medication to patients for uses other than those approved by

*. J.D. 2019, Washington University School of Law.

1. Coleen Klasmeier & Martin H. Redish, *Off-Label Prescription Advertising, the FDA and the First Amendment: A Study in the Values of Commercial Speech Protection*, 37 AM. J.L. & MED. 315, 315 (2011).

2. Brian M. Blood, *Off-Label Promotion after United States v. Caronia*, 12 FIRST AMEND. L. REV. 593, 594 (2014) (noting off-label uses of FDA-approved medications involve use of the medication for treatment purposes not “specifically approved by the FDA and [that] do not contain instructions for use on the product’s packaging or label.”).

3. *Id.*

the FDA.⁴ Drug companies and other non-medical professionals, however, have traditionally been prohibited from engaging in any promotion or advertising of off-label uses for FDA approved medications.⁵ According to the FDA, such off-label promotion by non-medical professionals constitutes “misbranding”⁶ of the drug, which is expressly prohibited under the Food, Drug, and Cosmetic Act⁷ (“FDCA” or “the Act”).⁸

The FDA’s general prohibition on off-label promotion by non-medical professionals implicates First Amendment concerns. Commercial speech is entitled to constitutional protection unless it is “false or misleading.”⁹ Given the protection of commercial speech otherwise, the FDA’s broad restriction on off-label promotion by non-medical professionals has given rise to an important question in the healthcare system: Whether the First Amendment restricts the FDA from proscribing the promotion and advertisement of off-label uses by non-medical professionals.

This Note will address how to properly determine, from a First Amendment standpoint, when commercial speech in the form of off-label drug promotion by pharmaceutical companies is “false or misleading” and thus may be permissibly regulated by the FDA without infringing on First

4. Proposed New Drug, Antibiotic, and Biologic Drug Regulations, 48 Fed. Reg. 26,733 (proposed June 9, 1983) (to be codified at 21 C.F.R. pt. 312). *See also* United States v. Caronia, 703 F.3d 149, 153 (2d Cir. 2012) (noting “the FDA generally does not regulate how physicians use approved drugs.”).

5. Klasmeier & Redish, *supra* note 1, at 317-18 (physician-prescribed off-label uses for certain medications constitute lawful and widely accepted medical practice recognized by the FDA).

6. 21 U.S.C. §352(a)(1) (2018). The FDCA provides that a drug is considered “misbranded” where “its labeling is false or misleading in any particular.”

7. Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. § 301 *et seq.*).

8. 21 U.S.C. § 331(a) – (c) (2018). The FDCA explicitly prohibits the misbranding of drugs, the introduction of misbranded drugs into interstate commerce, and the receipt and/or delivery of misbranded drugs for payment. *Id.*

9. Virginia Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc., 425 U.S. 748, 770-72 (1975) (holding that false or misleading commercial speech is not entitled to First Amendment protection); *see also* Cent. Hudson Gas & Elec. Corp. v. Public Serv. Comm’n, 447 U.S. 557, 562-63 (1980). Courts distinguish between commercial speech, “traditionally subject to government regulation,” and other forms of speech in that “[t]he Constitution [] accords a lesser protection to commercial speech than to other constitutionally guaranteed expression.” *Id.*

Amendment rights.¹⁰ In determining the constitutionality of restrictions on commercial speech that is not “false or misleading” under the First Amendment, courts balance the nature of the restricted expression with the governmental interest in restricting that expression.¹¹ Rather than focusing on the mechanics of balancing government interests with those of pharmaceutical manufacturers, this Note will focus on the narrow issue of how to accurately and fairly assess the threshold question of whether commercial speech in the context of off-label drug promotion is “false or misleading,” specifically, what constitutes “misleading.”

To accomplish this goal, it is important to understand the development of regulatory off-label drug promotion. Part I of this Note examines the development of off-label drug promotion and the current regulatory structure for off-label promotion by drug companies. Part II evaluates and critiques the changes in the commercial speech doctrine and its impact on off-label promotion. It also explains why judicial deference to either the government or drug companies in these cases is problematic. Part III discusses the need to adjust the manner in which the First Amendment issues of commercial speech are assessed in the context of off-label promotion by non-medical professionals and proposes a solution to adequately resolve the problems discussed in Parts I and II. The adjustment would occur at the threshold level of how to determine whether pharmaceutical companies’ off-label promotion and advertisement of drugs is “false or misleading.” This Note proposes that a viable, independent agency should be established as an intermediary between the FDA and pharmaceutical companies, whose function is to objectively

10. The scope of this Note is limited only to a discussion of how to properly determine whether off-label promotion is “misleading,” and who should make that determination. However, it is important to note that even where commercial speech is determined to be truthful and not misleading, the government may still regulate such speech, although its power to do so is more “circumscribed” and subject to stricter judicial scrutiny. *See Cent. Hudson Gas.*, 447 U.S. at 565. The government may regulate truthful and non-misleading speech by establishing (1) that it has a substantial interest in regulating such speech and (2) that the government’s regulation is in proportion to that interest and directly advances the government’s goals. *Id.*

11. *Cent. Hudson Gas.*, 447 at 563.

validate, or discredit, both the claims made by drug companies with respect to off-label uses, and FDA claims that such off-label uses are “false or misleading.” This proposal functions as a middle ground that addresses the interests of both the FDA and drug manufacturers by protecting the public from inaccurate off-label promotion and maintaining the First Amendment rights of drug manufacturers to engage in commercial speech.

I. FEDERAL REGULATORY LAW OF OFF-LABEL PROMOTION

With respect to commercial speech in the context of drug marketing and promotion by pharmaceutical companies, the threshold issue of whether such commercial speech is “false or misleading” has been a difficult issue for the courts to address and there is little precedent addressing how to define “misleading” in the context of off-label drug promotion.¹² Section A discusses the development of the law and the current regulatory structure for the manufacture and promotion of new drugs under the Federal Food and Drug Administration (“FDA”). Section B discusses case law concerning the general analysis of commercial speech under the First Amendment and its application to off-label promotion by pharmaceutical companies.

A. History & Development of Off-Label Promotion

The FDCA¹³ regulates activities relating to the manufacture and distribution of drugs and food in order to protect consumers and promote

12. Marc J. Scheineson & Guillermo Cuevas, *United States v. Caronia The Increasing Strength of Commercial Free Speech and Potential New Emphasis on Classifying Off-Label Promotion as “False and Misleading,”* 68 FOOD & DRUG L. J. 201, 212 (2013) (noting lack of legal or case law precedent in defining “misleading”).

13. Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. § 301 *et seq.*).

public health.¹⁴ With respect to drugs, the FDCA prohibits the introduction of any “new drug,” as it is defined under the FDCA,¹⁵ into interstate commerce unless an application has been filed and approved by the FDA.¹⁶ In other words, FDA approval is required for “each individual product that falls within the ‘new drug’ definition.”¹⁷ The FDCA defines “new drug” as “any drug . . . not generally recognized, among experts . . . as safe and effective for use under the condition prescribed.”¹⁸ Pursuant to the FDCA’s definition of “new drug,” any new use of a drug already approved by the FDA for a different use requires drug companies to file additional and separate applications.¹⁹ Thus, even where a drug is already FDA-approved for a particular use, additional FDA approval is required for any new use of that drug.

When seeking to introduce a drug²⁰ into the market, drug companies must file a “New Drug Application” (“NDA”) to be approved by the Secretary of Health and Human Services.²¹ The approval process for a “new drug” is initiated once drug manufacturers file the NDA, but final approval of the NDA could take up to fifteen years and cost over \$1 billion.²² Moreover, it is extremely rare that any potential drug submitted

14. 21 U.S.C. § 331(a) – (eee) (2018) (outlining specific acts prohibited under the FDCA).

15. 21 U.S.C. § 321(p)(1) (defining “new drug” as “any drug . . . not generally recognized, among experts . . . as safe and effective for use under the condition prescribed”).

16. 21 U.S.C. § 344(a) (providing that new drugs shall not be introduced into interstate commerce “unless an approval of an application filed pursuant to [the relevant FDCA provisions] is effective with respect to such drug”).

17. PETER BARTON HUTT, RICHARD A. MERRILL & LEWIS A. GROSSMAN, *FOOD AND DRUG LAW* 576 (Foundation 3rd ed. 2007).

18. 21 U.S.C. § 321(p)(1).

19. HUTT, MERRILL & GROSSMAN, *supra* note 17.

20. Generally, a produce is considered a drug if it is either “intended for use in the diagnosis, cure, mitigation, treatment, or prevention” of a disease or it “intended to affect the structure or function of the body.” HUTT, MERRILL & GROSSMAN, *supra* note 17, at 41.

21. 21 U.S.C. §355(b). An NDA is defined as the “vehicle through which drug sponsors formally propose that [the FDA] approve a new pharmaceutical for sale and marketing.” *FDA ATC Glossary*, FDA, <https://www.accessdata.fda.gov/scripts/cder/training/otc/topic2/images/Glossary.pdf> (last visited March 19, 2019).

22. HUTT, MERRILL & GROSSMAN, *supra* note 17, at 577. *See also* Blood, *supra* note 2, at 593-94 (recognizing that getting a new drug approved by the FDA “can take as long as twelve years and cost

for clinical testing actually end up gaining FDA approval.²³ Before a drug is approved, drug companies must undergo several different phases of rigorous studies and clinical trials²⁴ proving the safety and efficacy of the drug by establishing “substantial evidence”²⁵ that the drug’s effect is consistent with its proposed, “intended use.”²⁶ “Intended use”²⁷ under the FDCA refers to “the objective intent of the persons legally responsible for the labeling of drugs” as reflected through “oral or written statements by such persons or their representatives” and “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.”²⁸ After substantial evidence of the drug’s efficacy and safety for its intended use is established, FDA approval may be granted and only then may drug manufacturers incorporate their proposed use on the drug’s label and market the drug for that intended use.²⁹

Once a particular drug is federally approved, prescribing physicians may lawfully administer the drug to their patients “for both FDA-approved

more than \$500 million.”).

23. HUTT, MERRILL & GROSSMAN, *supra* note 17, at 624 (noting that out of “every 5,000 chemicals screened” through the IND’s preclinical testing, “five will proceed to clinical testing and one will survive to approval of an NDA.”).

24. 21 U.S.C. § 355(b)(5)(B); HUTT, MERRILL & GROSSMAN, *supra* note 17, at 628.

25. 21 U.S.C. § 355(d) defines “substantial evidence” as “evidence consisting of adequate and well-controlled investigation, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling[.]”

26. 21 U.S.C. § 355(d) (stating the grounds for refusing application “[i]f the Secretary finds...that the [New Drug Application does] not include adequate tests by all methods reasonably applicable to show whether...such a drug is safe for use under the conditions prescribed, [] or suggested in the proposed labeling...[or] the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions”).

27. 21 C.F.R. § 201.128 (2018). For examples of different ways to determine “intended use,” see 21 CFR 201.128.

28. 21 C.F.R. § 201.128.

29. 21 C.F.R. § 201.100(c)(2).

and unapproved uses.”³⁰ The FDA acknowledges the value of allowing physicians to prescribe medications for off-label uses;³¹ physicians act in the best interests of the patient and so must be allowed to use their medical knowledge and professional judgment in deciding how, when, and for what purpose a particular drug should be administered to a patient.³² Over time, drug manufacturers began to rely heavily on the prescribing behavior of physicians to administer certain drugs for off-label uses as an alternative to seeking FDA approval for a “new drug.”³³

However, unlike medical doctors, drug manufacturers are legally required to notify the FDA of any new drugs they seek to promote, which include a new use of any drugs already approved by the FDA.³⁴ Specifically, pharmaceutical companies must notify the FDA of “each change in each condition established in an approved NDA beyond the variations already provided for in the NDA.”³⁵ Therefore, in order to lawfully promote an FDA-approved drug for a new use, which includes the drug’s application for a new use, dosage, or population, drug manufacturers must submit a “Supplemental New Drug Application” (“SNDA”).³⁶ The SNDA subjects the drug to additional clinical trials aimed to establish the safety and efficacy of the drug’s proposed new use.³⁷

30. *United States v. Caronia*, 703 F.3d 149, 153 (2d Cir. 2012) (noting “the FDA generally does not regulate how physicians use approved drugs”).

31. *Klasmeier & Redish*, *supra* note 1, at 318.

32. *Id.*

33. *Id.* at 594-95. “An estimated twenty-one percent of prescriptions nationwide are for off-label uses, indicating that a significant portion of a manufacturer’s revenues...are through off-label prescribing.” *Blood*, *supra* note 2, at 594-95.

34. 21 C.F.R. § 314.70 (b) (2017).

35. 21 C.F.R. § 314.70 (a)(1)(i) (2017).

36. *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196, 203-04 (S.D.N.Y. 2015) (citing 21 C.F.R. § 314.70(b)); *See also*, Agata Dabrowska & Susan Thaul, *How FDA Approves Drugs and Regulates Their Safety and Effectiveness*, CONGRESSIONAL RESEARCH SERVICE (May 8, 2018), <https://fas.org/sgp/crs/misc/R41983.pdf>. “In order to make a change to an approved NDA—for example, to change the labeling, manufacturing process, or dosing, or to add a new indication (i.e., new use)—the manufacturer must submit a supplement (also referred to as a supplemental NDA). *Id.* at 8.

37. *Id.*

Drug manufacturers are prohibited from promoting the drug for that new use “[u]ntil the FDA has approved the new use.”³⁸

Under the current law, the FDA allows off-label promotion under one limited exception: in conjunction with a drug company’s participation in the Investigational New Drug (“IND”) application program. While the FDCA generally prohibits the introduction of any new unapproved drug into interstate commerce,³⁹ the Act contains an explicit exception allowing drugs to be transported “for the limited purpose of conducting clinical investigations.”⁴⁰ This exception allows drugs to undergo the IND program, which involves initial “screening studies,” conducted very early in the approval process, “prior to the traditional dose escalation, safety, and tolerance studies.”⁴¹ The IND process allows drug companies to share information and findings of a drug with independent medical professionals and other qualified persons only during this initial stage.⁴² In all other circumstances, any “new drug” must be approved by the FDA and undergo a premarket review through the FDA’s highly structured licensure process mandating that certain requirements and procedures be satisfied before a drug can be approved for a specific use.⁴³

Although there is no statutory provision expressly prohibiting off-label drug promotion by pharmaceutical companies, federal drug advertising and marketing regulations,⁴⁴ and certain provisions in the FDCA have been relied on by the FDA to suggest that such off-label promotion is prohibited, such as the “prohibited acts” section of the FDCA.⁴⁵ For instance, under FDA advertising regulations, “advertising cannot

38. *Amarin Pharma*, 119 F. Supp. 3d at 204.

39. 21 U.S.C. § 505(a).

40. HUTT, MERRILL & GROSSMAN, *supra* note 17, at 624 (citing 21 U.S.C. § 505(i)).

41. HUTT, MERRILL & GROSSMAN, *supra* note 17, at 628-29.

42. HUTT, MERRILL & GROSSMAN, *supra* note 17, at 624.

43. *United States v. Caronia*, 703 F.3d 149, 153 (2d Cir. 2012) (stating “[t]o obtain FDA approval, drug manufacturers are required to demonstrate, through clinical trials, the safety and efficacy of a new drug for each intended use or indication.”).

44. Codified in 21 C.F.R. § 202.

45. 21 U.S.C. § 331(a)-(c).

recommend or suggest any use that is not in the labeling in an approved NDA.”⁴⁶ Moreover, the government has brought lawsuits against pharmaceutical companies for such activities pursuant to the FDCA’s “prohibited acts” provision, which forbids the “misbranding” of drugs.⁴⁷ Under the FDCA, a misbranding violation can occur under a number of different circumstances relating to the packaging form, contents of the label and prominence of information on the label.⁴⁸ A drug will be deemed “misbranded if its labeling does not contain ‘adequate directions for use.’”⁴⁹ The law defines “adequate directions for use” as “directions under which the layman can use a drug safely and for the purposes for which it is intended.”⁵⁰ With respect to off-label drug promotion, “misbranding” violations for inadequate directions for use claimed by the FDA against pharmaceutical companies are generally based on either (1) “false or

46. HUTT, MERRILL & GROSSMAN, *supra* note 17, at 545 (citing 21 C.F.R. § 202.1(e)(4)).

47. 21 U.S.C. § 331(a)-(c); *See also* Klasmeier & Redish, *supra* note 1, at 319-20 (noting that the FDA justifies banning off-label promotion by arguing that it violates the FDCA on three grounds: [1] “it constitutes false or misleading labeling;” [2] “that it causes an approved new drug to become an unapproved new drug...thus triggering the requirement of FDA approval anew;” and [3] such promotion “misbrands the drug because it ‘is evidence of’ a new ‘intended use’ for which ‘adequate directions’ necessarily would be lacking in labeling by virtue of the unapproved status of the use”).

48. 21 U.S.C. § 352(a)-(n). Although misbranding under the FDCA can occur in a number of different forms, the scope of this Note is limited to the specific forms of misbranding most commonly applied in the context of off-label promotion by pharmaceutical companies

49. *Amarin Pharma v. FDA*, 119 F. Supp. 3d 196, 203 (S.D.N.Y. 2015). *See also* 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), [hereinafter, FDA DRAFT GUIDANCE], <https://www.fda.gov/regulatoryinformation/guidances/ucm125126.htm>. “An approved drug that is marketed for an unapproved use (whether in labeling or not) is misbranded because the labeling of such drug does not include ‘adequate directions for use.’”

50 21 C.F.R. § 201.5. Directions for use may be found inadequate for various reasons relating to the omission or inaccuracy of particular labeling content. *See* 21 U.S.C. § 352 (b)-(n); 21 C.F.R. §201.5 (stating inadequate directions for use may result from the following non-exhaustive reasons, “omission, in whole or in part, or incorrect specification of: (a) Statements of all conditions, purposes, or uses for which such drug is intended,...(b) Quantity of dose,...(c) Frequency of administration of application, (d) Duration of administration or application, (e) Time of administration or application... (f) Route or method of administration or application, [or] (g) Preparation for use[.]”).

misleading” advertising,⁵¹ or (2) failure to adhere to drug-labeling requirements related to the adequacy of a drug’s directions for its “intended use.”⁵² The FDA has interpreted the FDCA to prohibit the marketing of non-FDA approved new uses for FDA approved drugs because such marketing fails to provide “adequate directions for use,” thus constituting “misbranding.”⁵³ Under the definition of “intended use,”⁵⁴ intended use of a drug can be demonstrated through promotional statements made by a drug company,⁵⁵ meaning that “off-label promotional statements could thus presumably constitute evidence of an intended use of a drug that the FDA has not approved.”⁵⁶ Therefore, where an FDA-approved drug “is marketed for an unapproved use (whether in labeling or not),” the FDA considers the drug to be “misbranded” for failure to include “adequate directions for use.”⁵⁷ By law, the misbranding or sale of misbranded products is criminal violation, subjecting violators to up to three years in prison and/or a fine of \$10,000.⁵⁸

Today, the FDA continues to maintain this position, claiming that “any manufacturer dissemination of information relating to an off-label use represents a presumptive statutory violation.”⁵⁹ In recent years however, a number of courts have begun to recognize that the promotion of off-label use by pharmaceutical manufacturers is a form of commercial speech, entitled to protection under the First Amendment.⁶⁰

51. 21 U.S.C. § 352(a).

52. 21 U.S.C. § 352(f). *United States v. Caronia*, 703 F.3d 149, 162 (2d Cir. 2012).

53. *United States v. Caronia*, 703 F.3d 149, 155 (2d Cir. 2012).

54. *See supra* note 28 and accompanying text.

55. 21 C.F.R. § 201.128.

56. *United States v. Caronia*, 703 F.3d 149, 155 (2d Cir. 2012).

57. *Id.* (citing FDA, Draft Guidance).

58. 21 U.S.C. § 333(a)(2).

59. *Klasmeier & Redish*, *supra* note 1, at 326.

60. U.S. CONST. amend. I.

B. Commercial Speech and the Supreme Court

The First Amendment⁶¹ protects various forms of speech from government regulation, affording different levels of protection to different types of speech. Where a government regulation aims to limit or prohibit speech based on its content, the regulation is subject to “strict scrutiny,” and the government is required to show that the regulation is narrowly tailored to serve a substantial government interest.⁶² However, regulation of non-content based speech and commercial speech receive less protection under the First Amendment and are subject to “intermediate scrutiny.”⁶³ Commercial speech is defined as “expression related solely to the economic interests of the speaker and its audience,” and is viewed as “proposing a commercial transaction.”⁶⁴

In *Virginia Bd. of Pharmacies*,⁶⁵ the Supreme Court expanded First Amendment protection to purely economic forms of speech. There, the plaintiffs, a Virginia resident with a medical condition which required her to take prescription drugs on a daily basis and two nonprofit organizations, brought suit against the Virginia State Board of Pharmacy in order to challenge a Virginia statute that prohibited pharmacists from advertising prescription drug prices to the public.⁶⁶ The plaintiffs argued that such a ban was unconstitutional because the First Amendment entitles consumers

61. U.S. CONST. amend. I.

62. *Caronia*, 703 F.3d at 163 (noting that for content-based speech, the regulation must be “narrowly tailored to serve or promote a compelling government interest”). “Content-based government regulations on speech are ‘presumptively invalid.’” *Id.*

63. *Id.* at 163. See *Pearson v. Shalala*, 164 F.3d 650, 657 (D.C. Cir. 1999) (citing *Bd. of Trs. v. Fox*, 492 U.S. 469, 480 (1989)) (Noting that the level of scrutiny applied to the final step of the *Central Hudson* test does not require that ‘the manner of restriction is absolutely the least severe’...but only that the fit between the legislature’s ends and means is a ‘reasonable’ one.”).

64. *Cent. Hudson Gas & Elec. Corp. v. Public Serv. Comm’n*, 447 U.S. 557, 561-62 (1980). “The First Amendment...protects commercial speech from unwarranted governmental regulation.” *Id.* (citing *Virginia Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748, 761-62 (1975)).

65. *Virginia Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748 (1975).

66. *Id.* at 749, 753.

of prescription drugs to obtain “information that pharmacists wish to communicate to them through advertising and other promotional means, concerning the prices of such drugs.”⁶⁷ The defendant proffered several justifications for the ban, all of which focused primarily on the state’s interests in maintaining the professionalism of licensed pharmacists.⁶⁸ The defendant argued that allowing pharmacies to engage in price advertising will jeopardize their customers’ health because “aggressive price competition” will prevent pharmacists from supplying professional services in the compounding, handling and dispensing of prescription drugs.⁶⁹

The Supreme Court found that the defendant’s justifications were insufficient to justify the suppression of prescription drug price information.⁷⁰ The Court held that speech does not lose its constitutional protection under the First Amendment just because it is in the form of commercial speech.⁷¹ Therefore, the promotional information of pharmacists regarding drug prices, though purely commercial, is a form of protected expression.⁷² The Court emphasized the importance of fully informed consumers and the “free flow of commercial speech” as invaluable to promoting the public interest because “people will perceive their own best interests if only they are well enough informed, and [] the best means to that end is to open the channels of communication rather than to close them.”⁷³ Therefore, “[e]ven an individual advertisement, though entirely ‘commercial,’” must be protected to ensure the free flow

67. *Id.* at 766.

68. *Id.* at 766.

69. *Id.* at 767.

70. *Id.* at 770.

71. *Id.* at 762. “[T]hat the advertiser’s interest is a purely economic one . . . hardly disqualifies him from protection under the First Amendment.” *Id.*

72. *Id.*

73. *Id.* at 770. “[T]he particular consumer’s interest in the free flow of commercial information . . . may be as keen, if not keener by far, than his interest in the day’s most urgent political.” *Id.* at 763.

of commercial information.⁷⁴ However, while the Court expanded First Amendment protection to purely commercial speech, it also expressly qualified this protection, by establishing that commercial speech may be permissibly regulated under certain circumstances where the relevant commercial speech is “false or misleading.”⁷⁵

The Supreme Court noted that the impact of suppressing prescription drug price information would have a disproportionately worse impact on the poor, sick, and elderly, all of whom tend to spend the most on drugs “yet they are the least able to learn, by shopping from pharmacist to pharmacist, where their scarce dollars are best spent.”⁷⁶ Even “tasteless and excessive” advertising, according to the Court, constitutes “the dissemination of information as to who is producing and selling what product, for what reason, and what price,” which helps informed consumers make educated decisions.⁷⁷ The Court explained the indispensability of commercial speech in a free market economy, because “the allocation of our resources . . . will [primarily] be made through numerous private economic decisions,” and there is a legitimate public interest that those decisions are made intelligently.⁷⁸

In 1980, the Supreme Court in *Central Hudson*⁷⁹ established a new, four-part test governing the constitutionality of regulations in commercial speech (the “*Central Hudson Test*”).⁸⁰ Under the *Central Hudson Test*, government restrictions on commercial speech will be upheld based on a balancing of four criteria: (1) whether the commercial speech “concern[s]

74. *Id.* at 764. The Court listed examples of individual advertisements that are of “general public interest” based on prior cases: “advertisements stating that referral services for legal abortions are available; . . . a domestic producer advertises his product as an alternative to imports that tend to deprive American residents of their jobs . . .”

75. *Id.* at 770-72.

76. *Id.* at 763-64. “When drug prices vary as strikingly as they do, information as to who is charging what becomes more than a convenience. It could mean the alleviation of physical pain or the enjoyment of basic necessities.”

77. *Id.* at 765.

78. *Id.*

79. *Cent. Hudson Gas & Elec. Corp. v. Public Serv. Comm’n*, 447 U.S. 557 (1980).

80. *Id.* at 566.

lawful activity” and is not “misleading”; (2) whether the government has a “substantial interest” in regulating such speech; (3) whether “the regulation directly advances the governmental interest asserted”;⁸¹ and (4) whether “it is not more extensive than is necessary to serve that interest.”⁸²

The *Central Hudson* Court emphasized the importance of protecting commercial speech under the First Amendment because of the “informational function” of advertising, which “assists consumers and furthers the societal interest in the fullest possible dissemination of information.”⁸³ Even where an advertisement is “incomplete” and lacks all relevant facts, “the First Amendment presumes that some accurate information is better than no information at all.”⁸⁴ While recognizing that commercial speech is afforded constitutional protection under the First Amendment, the Supreme Court explicitly distinguished commercial speech from other forms of speech, in that the former is “traditionally subject to government regulation,” and is therefore entitled to less protection than “other constitutionally guaranteed expression.”⁸⁵

Therefore, in determining whether commercial speech regulations are afforded any constitutional protection, the courts, pursuant to the *Central Hudson Test*, must initially address whether the commercial speech “concern[s] lawful activity” and is not “misleading.”⁸⁶ Where commercial speech is “more likely to deceive the public than to inform it” or “relate[s] to illegal activity,” the government is permitted to regulate or ban that speech without giving rise to constitutional concerns.⁸⁷ Only once this

81. *Id.* at 565.

82. *Id.* at 566.

83. *Cent. Hudson Gas & Elec. Corp.*, 447 U.S. at 561-62.

84. *Id.* at 562.

85. *Id.* In making this distinction, the Court noted that First Amendment protection of non-content-based regulation or purely commercial speech was determined by the Court to be assessed under an “intermediate level of scrutiny.”

86. *Id.* at 566.

87. *Id.* at 563-64. “[T]here can be no constitutional objection to the suppression of commercial messages that do not accurately inform the public about lawful activity. The government may ban forms of communication more likely to deceive the public than to inform it.”

initial determination of false or misleading is made, does the court assess the remaining three prongs of the *Central Hudson* test: (1) whether the government has a “substantial interest” in regulating such speech; (2) whether “the regulation directly advances the governmental interest asserted”;⁸⁸ and (3) whether the regulation “is not more extensive than is necessary to serve that interest.”⁸⁹ For a regulation to satisfy the third prong, it must be proportionate to the state’s substantial interest, which requires “[t]he limitation on expression must be designed carefully to achieve the State’s goal.”⁹⁰ To do this, two criteria must be met: (1) “the restriction must directly advance the state interest;” and (2) there must be no alternative “more limited restrictions” that can equally serve the governmental interest.⁹¹ Although the majority did not specify the level of scrutiny applied in determining whether the commercial speech was protected under the First Amendment, Justice Blackmun’s concurrence described it as being “subject to an intermediate level of scrutiny.”⁹²

After *Central Hudson*, the commercial speech doctrine created in *Virginia Board of Pharmacies*⁹³ continued to develop in subsequent Supreme Court cases, while still applying varying levels of judicial scrutiny and deference to the government.⁹⁴

88. *Id.* at 565.

89. *Id.* at 566.

90. *Id.* at 564.

91. *Id.*

92. *Id.* at 573 (Blackmun, J., concurring) (“this level of intermediate scrutiny is appropriate for a restraint on commercial speech designed to protect consumers from misleading or coercive speech.”).

93. *See supra* notes 65-78 and accompanying text.

94. *See, e.g.,* *Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 511 (1996). In striking down a statute prohibiting the advertisement of alcohol, the Court held that the Government may not restrain speech concerning legal activity, even though it may have the power to prohibit that activity. *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 371-72 (2002). The Court relied on a strict interpretation of the last prong in *Central Hudson’s* commercial speech test to mean that any regulation restricting commercial speech must be narrowly tailored to serve the government’s substantial interest and there must be no alternative ways “that [do] not restrict speech, or that restricts less speech,” in which the Government could serve its interest. *Contra, e.g.,* *In re Primus*, 436 U.S. 412, 438 (1978). The Court adopted a more lenient interpretation that the restrictions be “reasonable...with respect to [] time, place and manner” of the speech.” *See also* *Virginia Bd. of Pharmacies v. Virginia Citizens Consumer Council*,

Recently, federal district and circuit courts are upholding off-label promotion by pharmaceutical companies and other non-medical professionals as commercial speech protected under the First Amendment.⁹⁵ In *Pearson v. Shalala*,⁹⁶ the D.C. Circuit Court addressed off-label advertising by marketers for diet supplements.⁹⁷ There, marketers sought FDA authorization for health claims in a dietary supplement's labeling, linking its consumption to reduced risk of certain diseases.⁹⁸ In its analysis, the D.C. Circuit distinguished between speech that is "inherently misleading"⁹⁹ and "potentially misleading."¹⁰⁰ Where commercial speech contains factual information conveyed in a misleading way, so as to "potentially mislead" consumers, the Court's *Central Hudson* analysis does not end as it would if the information were "inherently" misleading, but instead requires continued assessment of the remaining three prongs of the *Central Hudson* test to determine if the relevant commercial speech may be regulated.¹⁰¹ With respect to the fourth prong of the analysis, rather than requiring the government to show it exercised the least restrictive means in achieving its goal, the *Shalala*

425 U.S. at 771; *IMS Health Inc. v. Sorrell*, 630 F.3d 263, 279 (2d Cir. 2010) (quoting *Greater New Orleans Broad. Ass'n v. United States*, 527 U.S. 173, 188 (1999) ("The Government...must demonstrate narrow tailoring of the challenged regulation to the asserted interest -- a fit that is not necessarily perfect, but reasonable.")).

95. See, e.g., *Pearson v. Shalala*, 164 F.3d 650, 651 (D.C. Cir. 1999) (diet supplementary marketers seeking FDA authorization for health claims in a dietary supplement's labeling, linking consumption to reduced risk of certain diseases); see also *IMS Health Inc. v. Sorrell*, 630 F.3d 263, (2d Cir. 2011); *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012); *Amarin Pharma, Inc. v. United States FDA*, 119 F. Supp. 3d 196 (S.D.N.Y. 2015); *United States v. Vascular Solutions, Inc.* 181 F. Supp. 3d 342 (W.D. Tex. 2016).

96. *Pearson v. Shalala*, 164 F.3d 650.

97. *Id.* at 651.

98. *Id.*

99. *Id.* at 657. Advertising is inherently misleading where the information promoted is "subject to abuse" and cannot be presented in a way that is not "deceptive" to the general public. An example of an inherently misleading advertisement is one that "conveys no factual information."

100. *Id.* "Potentially misleading information" exists where "the information also may be presented in a way that is not deceptive."

101. *Id.* at 659. However, the Court gave deference to the FDA with respect to drafting necessary disclaimers to be included in labels found by the court to be potentially misleading.

Court only required that the regulation be a “‘reasonable’ means to achieve the government’s goals.”¹⁰² This somewhat differs from the approach taken in *Central Hudson*, in which the Court held restrictions on commercial speech to be unconstitutional “if the government’s interest could be served as well by a more limited restriction.”¹⁰³

In 2010, the Second Circuit decision in *IMS Health v. Sorrell*¹⁰⁴ expanded First Amendment commercial speech protection to include the use of prescriber-identifiable data (“PI data”)¹⁰⁵ for purposes of pharmaceutical marketing.¹⁰⁶ The court struck down a Vermont statute prohibiting data miners¹⁰⁷ from selling PI data to pharmaceutical manufacturers, viewing the law as an attempt by Vermont’s legislature to interfere with and control “the marketplace of ideas in order to influence conduct.”¹⁰⁸ The Second Circuit held that “[s]peech in aid of pharmaceutical marketing . . . is a form of content-based expression protected by the Free Speech Clause of the First Amendment.”¹⁰⁹ Because the Court did not find the speech to be false or misleading, it went through the remaining prongs of the *Central Hudson* Test, focusing primarily on whether the regulation was proportional to the government’s interest in regulating the speech.¹¹⁰ The burden falls on the government to show that the restriction on prescriber-identifying information, a form of content-

102. *Id.* at 659.

103. *See supra* notes 90-91.

104. *IMS Health Inc. v. Sorrell*, 630 F.3d 263 (2d Cir. 2010).

105. *Id.* at 267. “PI data” refers to information about patients collected by pharmacies when filling out prescriptions for those patients, consisting of the prescriber’s name and address, the patient’s name, dosage, quantity of the drug, date and place the prescription is filled, and the patient’s age and gender.

106. *Id.*

107. *Id.* at 274. “[D]ata miners are in the business of aggregating and selling the data to pharmaceutical manufacturers . . . so that pharmaceutical manufacturers can use the data in their marketing strategies.”

108. *Id.* at 277.

109. *Sorrell v. IMS Health Inc.*, 564 U.S. 552, 557 (2011) (holding that state statutes enforcing content- and speaker-based restrictions are subject to heightened judicial scrutiny).

110. *IMS Health Inc. v. Sorrell*, 630 F.3d at 275.

based speech, proportionately serves the government's interest, requiring the government to show that the restriction "furthers at least one interest 'in a direct and material way,'"¹¹¹

On appeal, the Supreme Court affirmed the Second Circuit's decision holding that "[s]peech in aid of pharmaceutical marketing . . . is a form of content-based expression protected by the Free Speech Clause of the First Amendment."¹¹² Therefore, the burden is on the government to demonstrate that the law restricting that speech "is consistent with the First Amendment pursuant to the *Central Hudson* Test," which requires the government to show "at least that the statute directly advance[d] a substantial governmental interest and that the measure is drawn to achieve that interest."¹¹³ In applying *Central Hudson*, although the Court acknowledged that laws limiting content-based expression,¹¹⁴ even if purely commercial, are subject to a more heightened judicial scrutiny than non-content-based commercial speech,¹¹⁵ the Court did not specify which level of scrutiny applied in the particular case before it.¹¹⁶ Instead, the Court found that the restriction is "unconstitutional under the lesser intermediate standard set forth in *Central Hudson*,"¹¹⁷ and that the outcome would be "the same whether a special commercial speech inquiry or a

111. *Id.* at 291-92 (quoting *Edenfield v. Fane*, 507 U.S. 761, 767 (1993)).

112. *Sorrell v. IMS Health Inc.*, 564 U.S. 552, 557 (2011) (holding that state statutes enforcing content- and speaker-based restrictions are subject to heightened judicial scrutiny).

113. *Id.* at 571-72.

114. *United States v. Caronia*, 703 F.3d 149, 165 (2d Cir. 2012) (citing *Turner Broad., System, Inc. v. F.C.C.*, 512 U.S. 622, 643 (1994)). "Content-based" speech restriction defined as one that "distinguishes between 'favored speech' and 'disfavored speech on the basis of the ideas or views expressed.'"

115. *Sorrell v. IMS Health*, 564 U.S. at 553 (finding circumstances involving restrictions on content-based speech are "sufficient to justify applying heightened scrutiny even assuming that prescriber-identifying information is a mere commodity"). *See also, Id.* at 588 (Breyer, J., dissenting) (noting that the majority opinion applied "a standard yet stricter than *Central Hudson*").

116. *See United States v. Caronia*, 703 F.3d 149, 165 (2d Cir. 2012) (citing *Sorrell v. IMS Health, Inc.*, 564 U.S. 544, 553 (2011)) "The Court did not decide the level of heightened scrutiny to be applied, that is, strict, intermediate, or some other form of heightened scrutiny." *Id.* at 165,

117. *United States v. Caronia*, 703 F.3d 149, 164-65 (2d Cir. 2012).

stricter form of judicial scrutiny is applied.”¹¹⁸ The *Sorrell* Court explained that the purpose of these standards is to “ensure . . . that the State’s interests are proportional to the resulting burdens placed on speech [and] that the law does not seek to suppress a disfavored message.”¹¹⁹ The Supreme Court identified a possible alternative to the State’s restriction on pharmaceutical marketing, which accomplished the same goals but through means that were less restrictive and burdensome on constitutionally protected commercial speech.¹²⁰

C. Off-Label Promotion as Commercial Speech

*United States v. Caronia*¹²¹ was the first case to address whether the First Amendment protects truthful and non-misleading promotional statements of pharmaceutical companies against FDA misbranding claims.¹²² In *Caronia*, a specialty sales consultant engaged in the marketing of an FDA-approved drug to treat narcolepsy and known to cause serious side effects, for off-label uses to treat other illnesses including Parkinson’s and Multiple Sclerosis.¹²³ The FDA argued that the FDCA’s misbranding provisions prohibited off-label drug promotion by pharmaceutical manufacturers.¹²⁴ The court found that “the FDCA itself does not expressly prohibit or criminalize off-label promotion” of drugs as misbranding.¹²⁵ Instead, misbranding of a drug under the FDCA depends on “whether a drug’s labeling is adequate for its intended use, and the

118. *Sorrell v. IMS Health*, 564 U.S. at 553.

119. *Id.* at 560.

120. *Id.* at 571 (“[T]he State could have addressed physician confidentiality through ‘a more coherent policy.’ . . . For instance . . . by allowing the information’s sale or disclosure in only a few narrow and well-justified circumstances”) (internal citations omitted).

121. *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012).

122. *Amarin Pharma, Inc. v. U.S. Food and Drug Admin.*, 119 F. Supp. 3d 196, 208 (S.D.N.Y. 2015).

123. *Caronia*, 703 F.3d at 156.

124. *Id.* at 162.

125. *Id.*

FDCA permits the government to prove intended use by reference to promotional statements made by drug manufacturers.”¹²⁶ Moreover, the Second Circuit emphasized that where it is unclear whether the promotion of a particular off-label use constitutes misbranding, the Court will “construe the FDCA narrowly to avoid a seriously constitutional question.”¹²⁷ In narrowly construing the FDCA, the court refused to interpret the Act’s misbranding provisions as “criminaliz[ing] the simple promotion of a drug’s off-label use by pharmaceutical manufacturers” because doing so “would run afoul of the First Amendment.”¹²⁸ Rather than attempting to prove misbranding by reference to Caronia’s promotional statements, the government “clearly prosecuted Caronia for his words – for his speech,” by claiming that Caronia’s off-label promotion, in and of itself, constituted misbranding.¹²⁹

After the determining that off-label promotion itself was not prohibited under the FDCA, the *Caronia* court assessed the constitutionality of restricting Caronia’s off-label promotion under the *Central Hudson* Test.¹³⁰ The court found the FDCA misbranding provisions to be “content- and speaker-based” and therefore, relying on the Supreme Court in *Sorrell*, applied a “heightened” level of scrutiny.¹³¹ Therefore, the court held that the government’s prosecution of Caronia would “unconstitutionally restrict free speech,” because nothing in the FDCA prohibited or criminalized “the truthful off-label promotion of [an] FDA-approved prescription drugs.”¹³²

In a decision addressing the misbranding provisions of the FDCA, the district court in *Amarin Pharma v. FDA* reaffirmed the Second Circuit’s decision in *Caronia* supporting the off-label promotion of truthful and

126. *Id.*

127. *Id.* at 162.

128. *Id.* at 162.

129. *Id.* at 161.

130. *Id.* at

131. *Id.* at 164-65.

132. *Id.* at 168. The Court limited its conclusion to “FDA-approved drugs for which off-label use is not prohibited.”

non-misleading statements and the application of the misbranding provisions of the FDCA.¹³³ Plaintiff Amarin Pharma Inc. (“Amarin”), a drug manufacturer, attempted to obtain FDA approval for two uses of Vascepa, a drug developed by the plaintiff to address cardiovascular issues.¹³⁴ Amarin first sought and eventually acquired the FDA’s approval to promote Vascepa as an aid in treating adults with “very high triglycerides,” which increases the risk that an individual will develop cardiovascular disease.¹³⁵ The initial use approved by the FDA was based on studies and clinical trials indicating the drug’s effectiveness in reducing “very high triglyceride levels,” which was shown to decrease the risk of cardiovascular disease for those patients.¹³⁶ Amarin subsequently sought approval to market a second use for the drug to treat individuals with “persistently high triglyceride” (PHT) levels (the “off-label use” at issue in this case).¹³⁷ The effectiveness of the drug in lowering triglycerides for those with PHT was shown pursuant to clinical trials under the FDA’s “special protocol assessment” program, in which the FDA “sets out the design and size parameters for clinical trials of a new drug, and the conditions under which the FDA would approve the drug.”¹³⁸ Despite Amarin’s compliance with the FDA’s standards and procedures, the government agency discovered subsequent evidence indicating “substantial uncertainty” as to whether Vascepa’s effectiveness in reducing triglycerides in patients with PHT levels reduced the risk of cardiovascular disease for those patients, as it did for patients with very

133. *Amarin Pharma, Inc. v. U.S. Food and Drug Admin.*, 119 F. Supp. 3d 196, 237 (S.D.N.Y. 2015). The Court granted a preliminary injunction preventing FDA prosecution of truthful and non-misleading statements after modification of the label’s text.

134. *Id.* at 209.

135. *Id.*

136. *Id.*

137. *Id.*

138. *Id.* at 210. “Provided that the manufacturer follows the procedure set in the SPA agreement and the drug . . . meets the benchmarks for effectiveness set in the agreement, the FDA must approve the drug,” except where “a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.”

high triglycerides, based on separate clinical trials showing no clear correlation between reduced triglycerides in patients with PHT and reduced risk of cardiovascular disease.¹³⁹ The FDA consequently denied Amarin's SDNA to market Vascepa the off-label use, warning that the drug "may be considered to be misbranded . . . if it is marketed with [the off-label use] before approval."¹⁴⁰ Amarin filed a complaint against the FDA, arguing that the FDA's threat of a misbranding action for the truthful statements Amarin sought to promote and include on Vascepa's label "chill[ed] it from engaging in constitutionally protected truthful speech."¹⁴¹ Although the government conceded to the truthfulness of the statements regarding the drug's ability to reduce triglyceride levels for those with PHT,¹⁴² it found the results of the clinical trial to be misleading to consumers because "the 'clinical rationale,' or premise, of the [clinical] study had been that reducing triglyceride levels in that population would reduce the risk of cardiovascular events."¹⁴³ According to the FDA, the label was potentially misleading, in that it "could cause a physician to prescribe Vascepa in lieu of [alternative treatments]" known to aid in cardiovascular health, despite the fact that subsequent studies indicated uncertainty as to the effectiveness of the drug in treating cardiovascular events.¹⁴⁴

The district court interpreted the Second Circuit's holding in *Caronia* to prohibit the government from bringing FDCA misbranding actions against drug manufacturers' truthful statements "promoting off-label use of an

139. *Id.* at 209.

140. *Id.* at 212.

141. *Id.* at 198.

142. *Id.* at 209. "It is undisputed that Vascepa is effective in reducing such triglyceride levels [for those with PHT] . . . as confirmed by the FDA in correspondence with Amarin."

143. *Id.* at 212. More specifically, Amarin's intended new use of the drug was to provide the same health benefit to a new group of patients, those with PHT, as it did to patients with severely high triglycerides, by performing the same medical function, i.e., reduced risk of cardiovascular related illnesses by way of reducing triglyceride levels.

144. *Id.* at 217.

FDA-approved drug.”¹⁴⁵ The court assessed the truthfulness of Amarin’s statements regarding the study testing Vascepa’s effect in reducing triglycerides for individuals with PHT, in large part, based on the FDA’s approval of the study and its written confirmation that Vascepa has been proven to reduce triglyceride levels for PHT individuals.¹⁴⁶ The court ultimately found Amarin’s proposed statements and disclosures on the drug’s label to be truthful and not misleading and therefore approved the use of those statements and disclosures, subject to modifications by the court.¹⁴⁷ For instance, the court replaced “benefit” in Amarin’s proposed statement to the phrase “benefit, if any,” in order to avoid leading doctors to “assume that some benefit has been found.”¹⁴⁸ The court agreed with the FDA with respect to certain modifications and additions as well, including a statement establishing that the FDA did not approve Vascepa for off-label use.¹⁴⁹ Relying on *Caronia*, the court found in favor of Amarin, holding that the manufacturer’s “truthful and non-misleading speech promoting the off-label use of Vascepa” was lawful and could not be the basis of a claim for misbranding.¹⁵⁰

The case law relating to off-label drug promotion and the constitutionality of regulations restricting this speech suggests that there is little clarity as to when drug companies can engage in off-label promotion and how to determine when such commercial speech is considered “misleading.” For instance, several cases discussed in this Note involve majority opinions that, while applying the intermediate level scrutiny required under *Central Hudson*, have applied some variation of this standard. This reflects the vagueness of the *Central Hudson* test and the

145. *Id.* at 226.

146. *Id.* at 229.

147. *Id.* at 232-36.

148. *Id.* at 232.

149. *Id.* However, the Court altered this statement in accordance with Amarin’s proposed alternative explanation, to state that there was “current uncertainty” as to cardiovascular benefits, as opposed to the FDA’s statement which the Court found implied that reducing triglycerides in patients with PHT has “been affirmatively shown *not* to reduce the risk of cardiovascular events.”

150. *Id.* at 237.

discretion we have given judges in determining whether off-label speech is misleading. This has important consequences under the law, because the whole legal structure of commercial speech is built around the idea of false and misleading speech. Therefore, establishing a legitimate way to classify the validity of off-label use promotion is an important predicate for determining the legal disposition of FDA claims against drug companies for “misleading” off-label speech.

D. Arguments For & Against FDA Restrictions on Off-Label Promotion

From the government’s point of view, unrestricted off-label drug promotion poses a significant threat to public safety due to its potential to misinform and mislead consumers.¹⁵¹ In fact, the Supreme Court has recognized the importance of the NDA process and the substantial government interest served by it, in which case such speech may constitutionally be regulated.¹⁵² According to the FDA, the interests of drug companies in pursuing off-label promotion, motivated by profit, are outweighed by the “substantial government interest” in public health and safety, which ensures that rigorous studies and evaluations of the safety and effectiveness of new drugs and uses for existing drugs are conducted.¹⁵³ From the government’s point of view, it is important to differentiate between the off-label prescribing behavior of physicians and the promotion of off-label uses by pharmaceutical companies, because in the latter situation, drug companies have a strong incentive to circumvent FDA approval, either to avoid the costs of conducting the required clinical trials, or because of fear that their new use would not satisfy the FDA’s standards.¹⁵⁴

151. Klasmeier & Redish, *supra* note 1, at 335 n. 98. “[A]dequate protection of the public health requires unwavering enforcement of the high standards for efficacy data in the 1962 drug amendments.”

152. *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 369 (2002).

153. *Id.*

154. Kathryn Bi, *What is “False or Misleading” Off-Label Promotion?*, 82 U. CHI. L. REV. 975,

At the same time, categorically banning off-label promotion that is neither false nor misleading violates the First Amendment protections of commercial speech.¹⁵⁵ From the perspective of drug manufacturers and many courts, First Amendment rights are “not compromised by the fact that the speaker is a corporate person or by the speaker’s pursuit of commercial advantage.”¹⁵⁶ However, some critics argue that although content-based restrictions on speech should be subject to heightened scrutiny in the interest of protecting free speech, the FDA’s restrictions on off-label promotion should be treated differently “due to off-label marketing’s potential to pose significant risks to patients.”¹⁵⁷

II. EVALUATING THE CURRENT LEGAL FRAMEWORK

Cases following the Supreme Court decision in *Virginia Bd. of Pharmacies*¹⁵⁸ reflect important trends that have led to the current legal framework for assessing commercial speech in the health care context. Although not explicitly stated by the majority, Justice Blackmun’s concurrence indicates that the *Central Hudson* majority applied an intermediate level of scrutiny in assessing the fourth prong of the *Central Hudson* Test.¹⁵⁹ However, the D.C. Circuit in *Pearson v. Shalala* redefined

978-79 (2015). This would lead to circumstances where “doctors who received information about off-label uses might...prescribe treatments that would not meet the FDA’s high approval standards.” *Id.* at 979.

155. *United States v. Caronia*, 703 F.3d 149, 152 (2d Cir. 2012). *See also* *Thompson v. W. States Med. Ctr.*, 535 U.S. 357 at 357 (citing *Cent. Hudson Gas & Elec. Corp. v. Public Serv. Comm’n*, 447 U.S. 557, 566 (1980)). In recognizing the value of the FDA’s rigorous drug approval process, the Supreme Court has consistently refused to provide the government unlimited authority in regulating such speech.

156. George W. Evans & Arnold I. Friede, *The Food and Drug Administration’s Regulation of Prescription Drug Manufacturer Speech: A First Amendment Analysis*, 58 *FOOD & DRUG L.J.* 365, 377 (2003); *See also* *Cent. Hudson Gas & Elec. Corp. v. Pub. Service Comm’n*, 447 U.S. 557, 580 (1980) (Stevens, J., and Brennan, J. concurring in judgment). The values of the First Amendment limited by “the economic motivation of a speaker.”

157. *Blood*, *supra* note 2, at 606-07.

158. *See supra* note 65.

159. *See supra* note 92. *See also*, *IMS Health Inc. v. Sorrell*, 630 F.3d 263, 290 (2d Cir. 2010)

the standard to require only that the restriction on commercial speech be “reasonable,” to achieve the government’s interest and end goal, despite the existence of alternative means.¹⁶⁰ In later cases, application of the *Central Hudson* Test reflected a trend by the Supreme Court favoring the protection of commercial speech over the government’s substantial interest in restricting that speech.¹⁶¹ The 2011 Supreme Court decision in *Sorrell v. IMS Health*¹⁶² served as the basis for subsequent decisions involving the promotion of off-label use by pharmaceutical companies, particularly the landmark decision made by the Second Circuit in *United States v. Caronia*.¹⁶³ In suggesting less restrictive alternatives, the *Sorrell* Court narrowed the scope of permissible governmental regulations on commercial speech by holding that state statutes limiting “content- and speaker-based” speech, even if purely commercial, are subject to a more “heightened” judicial scrutiny than initially established in *Central Hudson*.¹⁶⁴ The Court applies strict scrutiny by requiring that the means pursued by the government in restricting commercial speech must be drawn in a way that narrowly achieves the government’s asserted interest¹⁶⁵ which reflects a level of scrutiny distinguishable from requiring the means be “reasonable,” as was the case prior to *Pearson v. Shalala*.¹⁶⁶ However, the Court did not determine the specific standard applied and was unclear as to what level of heightened scrutiny was required.¹⁶⁷ The Second Circuit in *Caronia* and the Southern District of New York in *Amarin* seemed to rely on the *Sorrell* decision in requiring heightened

(“while *Central Hudson* compels a more searching review of a restriction on commercial speech than a restriction on pure conduct, it does not require strict scrutiny.”).

160. *Supra* note 103 and accompanying text

161. *See* cases cited *supra* note 95.

162. *See supra* note 109.

163. *Supra* text accompanying note 131.

164. *See supra* notes 115-116 and accompanying text.

165. *See supra* note 115 and accompanying text.

166. *See supra* text accompanying note 102.

167. The court does not specify what “heightened scrutiny” means, however it is described as being “stricter than *Central Hudson*.” *Sorrell v. IMS Health, Inc.*, 564 U.S. 552, 588 (2011) (Breyer, J. dissenting).

judicial scrutiny in assessing “content- and speaker-based” commercial speech. Based on these decisions and the standards applied by the courts in assessing commercial speech in general, one trend is clear: the extent of protection courts are willing to afford to commercial speech is increasing at the expense of federal restrictions on such speech in order to serve a substantial government interest. This kind of judicial positioning has led to a focus on the mechanics of balancing the competing interests of free speech and the government, which presumes truthful, non-misleading speech. However, as the doctrine of commercial speech has evolved, it is evident that the court has been unable to decide how to definitively assess commercial speech with respect to proper balancing of interests and level of scrutiny.¹⁶⁸

B. Impact of Commercial Speech on the Off-Label Drug Problem

The Courts place legitimate emphasis on protecting truthful commercial speech at the expense of government regulations in accordance with First Amendment values. However, to effectively ensure these constitutional values are served while also protecting the general public, it is important that the court place more emphasis on how to properly assess the threshold issue under the *Central Hudson* test: whether the commercial speech is misleading or concerns unlawful activity. The first step in any commercial speech analysis is to determine whether the speech at issue is entitled to constitutional protection under the First Amendment. Because “false” or “misleading” commercial speech is not protected under the First Amendment¹⁶⁹ the threshold question in any commercial speech analysis is whether the commercial speech “concern[s] lawful activity” and is not

168. The Supreme Court in *Sorrell v. IMS* stated, “did not decide the level of heightened scrutiny to be applied, that is, strict, intermediate, or some other form of heightened scrutiny.” *United States v. Caronia*, 703 F.3d at 164. See cases cited *supra* note 94.

169. *Virginia Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748, 770-72 (1975).

“misleading.”¹⁷⁰ Until *Amarin Pharma*,¹⁷¹ at least in the context of off-label promotion of FDA-approved prescription drugs, courts have been unclear as to what may constitute false or misleading commercial speech because courts generally presume the truthfulness of the speech to avoid constitutional questions.¹⁷² This reflects the strong proclivity of the courts to consistently place more value on free speech than governmental interests in order to preserve the constitutional guarantee of free speech. This is so even where there is a possibility that it may be false or misleading.¹⁷³ For instance, rather than considering whether Caronia’s off-label promotion was true and not misleading, the *Caronia* court presumed the statements to be true, despite potential ambiguity as to accuracy of the statements.¹⁷⁴ This decision further reflects the tendency of courts to narrow the scope of what may constitute as false or misleading, by assuming the truthfulness of the speech despite uncertainty as to its accuracy, and by placing the burden of proof on the government to conclusively establish the falsity of the speech.

The first prong of the *Central Hudson* test was finally addressed in *Amarin Pharma v. FDA*.¹⁷⁵ This case presents a more troubling issue with respect to the manner in which the accuracy of off-label statements is assessed, in that the Court focused heavily on the accuracy of the statements standing on their own, without considering the significant potential for the speech to mislead consumers when promoted under the particular circumstances of the case.¹⁷⁶ The FDA acknowledged the truthfulness of the relevant statements, but rightfully expressed concern that promoting the study’s results would mislead both physicians and patients with PHT.¹⁷⁷ Since the drug was already approved by the FDA as

170. *Supra* note 86 and accompanying text.

171. *Supra* note 133.

172. *See supra* text accompanying note 127.

173. *Supra* note 84 and accompanying text.

174. *Supra* text accompanying notes 127-128.

175. *See supra* notes 133-150.

176. *See supra* text accompanying note 146.

177. *See supra* notes 142 & 144 and accompanying text.

an aid in reducing the risk of cardiovascular disease by reducing triglyceride levels in those with “very high triglycerides,” there is reasonable concern that medical professionals, patients, and reasonable laypersons in general would view the results of the study on “persistently high triglycerides” to function in the same way.¹⁷⁸ Despite the validity of the FDA’s concerns, the Second Circuit took it upon itself to determine what disclosures and statements were misleading or not.¹⁷⁹ A determination of whether a particular medical statement or study is truthful or misleading falls outside the scope of the judiciary’s experience and knowledge. A judge is unable to accurately and intelligently determine the actual truthfulness or deceptiveness of statements requiring a deep professional understanding of the medical field and hard sciences. Additionally, it can also be argued that the *Amarin* Court relied too heavily on the truthfulness of the off-label statements standing alone, but failed to adequately consider how these statements may mislead consumers. Both the *Caronia* and *Amarin* decisions reflect the current judicial position on off-label promotion by pharmaceutical companies, which places emphasis on the importance of preserving the constitutional guarantee of free speech.

Providing the FDA with exclusive authority and total discretion to restrict off-label promotion unequivocally runs counter to First Amendment protections of free speech. Even with the permitted exception in place that allow off-label promotion in conjunction with a drug company’s participation in the IND application program, the FDA still retains the ability to conclusively prohibit off-label promotion in these contexts by independently deciding whether the speech is misleading or false.¹⁸⁰ The high costs and time-consumption characterizing the FDA approval process has effectively acted as a barrier to seeking approval, leading many drug manufacturers to rely on physician prescribing

178. See *supra* notes 142 and accompanying text.

179. See *supra* notes 146-150 and accompanying text.

180. *Supra* notes 14-19.

behavior as a less costly alternative.¹⁸¹ This onerous process ironically runs counter to the FDA's argument that it aims to promote public health¹⁸² because it hinders medical advancements and treatments for sick patients. As a whole, the regulations proposed by the FDA have been unnecessarily over-inclusive because they prevent drug manufacturers from promoting information to the public regarding safe off-label use to doctors who are already prescribing drugs that are off-label. By preventing drug companies from promoting safe and important information regarding new uses to doctors, FDA restrictions do not directly advance the agency's aim to protect the public's exposure to off-label uses. In fact, allowing drug companies to disseminate truthful and non-misleading statements that have undergone non-FDA, but equally rigorous, studies could help achieve the FDA objective of protecting the public by ensuring that new drugs and new uses for existing drugs are continuously being discovered and made available to consumers. Further, by not requiring manufacturers to gain re-approval from the FDA, drugs could be produced for new uses without increasing the cost of the drug, and potentially decreasing its cost, since the manufacturer can avoid paying millions of dollars for re-approval of an already approved drug.¹⁸³ Finally, giving drug companies the choice to not get re-approved by the FDA helps promote public health by allowing patients and physicians to be fully informed and make educated decisions. However, this framework could also result in the opposite, in the case where drug companies begin promoting off-label uses that are not adequately substantiated.

Despite the benefits of allowing off-label promotion by pharmaceutical companies, the courts' approach to dealing with the threshold issue places unwarranted trust in the drug companies, which is also dangerous to consumer protection. If the *Caronia* decision granting constitutional protection to off-label promotion by drug representatives were to be

181. *Supra* text accompanying note 33.

182. *See supra* note 151 and accompanying text.

183. *Supra* note 22 and accompanying text.

adopted nationwide, this would effectively allow drug manufacturers to place less concern on the truthfulness of the off-label marketing for their products.¹⁸⁴ Such deference to pharmaceutical manufacturers allows them to evade the FDA approval process and avoid performing the necessary clinical trials to fully substantiate the drug company's claims regarding off-label uses. This abuse of discretion by drug companies would result in wide-ranging harm that could be life threatening to huge populations of people. This is the case even if drug manufacturers are to be held liable after discovering an off-label use in fact causes serious health problems. Additionally, the courts' position in consistently finding in favor of drug companies without adequately questioning whether their off-label statements are misleading necessarily undermines the FDA's authority and position as a government agency, whose job is to ensure drugs are safe and effective for their intended use by regulating the development and dissemination of medical drugs and devices.

III. CUTTING THE GORDIAN KNOT: ACHIEVING A SOLUTION

The threshold in any case addressing the constitutionality of regulations limiting commercial speech is whether the relevant speech is false or misleading or concerns illegal activity. Yet most courts have placed little importance in assessing this factor, relative to the emphasis placed on the remaining three factors focused on governmental interests. Although a finding that particular commercial speech is "false" may arguably require a straightforward assessment, determining whether certain off-label drug promotion is "misleading" presents a significantly more difficult determination, especially since the Supreme Court in *Central Hudson* and *Sorrell* did not clearly define what constitutes "misleading" in the context of drug promotion by pharmaceutical companies. In order to assure that

184. Blood, *supra* note 2, at 608. "Should the holding in *Caronia*...be adopted by the Supreme Court...[t]he holding would, . . . in lieu of an alternative regulation scheme, free manufacturers and their representatives from liability for truthful off-label promotion and marketing."

both the interests of the government in protecting the public and the interest of drug manufacturers' in engaging in commercial speech are adequately served, we must shift the manner in which the threshold question is addressed by adjusting the way commercial speech is analyzed. This adjustment would occur at the threshold level of determining what evidence suffices to rebut the government's claim that commercial speech is "false or misleading."

This Note proposes a model for fairly and accurately assessing the threshold issue of the *Central Hudson* test through significant administrative changes that entail the creation of a mechanism curing the danger that these off-label promotions are in fact "false and misleading" while maintaining the integrity of the First Amendment in protecting free speech. Cutting the Gordian knot and achieving a good iteration and reliable First Amendment result of whether speech is false or misleading requires establishing a new, intermediary structure between the FDA and pharmaceutical companies.¹⁸⁵ This structure must be an independent non-governmental organization made up of medical professionals and scientists in the field, as well as marketing professionals, whose purpose is to monitor and review the clinical trials performed by drug manufacturers to establish evidence that suffices to objectively validate, or discredit, the claims made by drug companies. Marketing professionals will play an important role in testing and reviewing proposed off-label statements deemed to be "truthful," which includes engaging with ordinary consumers, both medical professionals and laypersons, to determine whether they are likely to be misled.

In order to guarantee a non-bias and objective determination is made by the entity, it is to be compensated a fixed amount annually, which would come from the revenues of each manufacturer that chooses to utilize the

185. Something similar to the independent, nonprofit Joint Commission, composed of physicians, administrators, nurses, and other experts, which evaluates and subsequently "accredits and certifies...health care organizations in the US." *Facts about the Joint Commission*, THE JOINT COMMISSION (July 8, 2016), https://www.jointcommission.org/facts_about_the_joint_commission/.

non-governmental agency. This compensation system would effectively prevent the reviewing agency from intentionally or inadvertently making decisions based on financial benefits. It would also incentivize the drug companies to engage in equally, if not more, rigorous clinical trials and studies to fully corroborate the claimed new use, to avoid having to pay the agency if the proposed new use is unsafe. This would be helpful to drug companies that may be able to adequately establish evidence supporting a proposed new use without the high cost and time commitments required by the FDA's approval process. Manufacturers will be able to do everything on their own time and as fast as they prefer, but will also have incentive to make sure the results of their non-FDA trials and studies provide solid evidence that will pass the muster of the independent agency's review standards. If this particular kind of private sector initiative comes into place, the Courts would rely on the external corroborating evidence of an independent third-party organization as sufficient to objectively establish that commercial speech is truthful and not misleading, and vice versa. The development of this non-governmental structure would encourage competition with the FDA, incentivizing the government agency to adjust its restrictions and standards or reduce the financial and time-consuming burdens on drug companies. The FDA should provide tax incentives or some other monetary benefit to incentivize manufacturers to pursue the FDA re-approval path for new uses, which could be equally or more beneficial financially, to both parties. Therefore, the development of the independent, non-governmental agency will also function to address the significant costs associated with the FDA's approval process. Although such a drastic administrative change would be difficult and costly to develop, both financially and with respect to it is certainly possible and functions as a viable alternative to the existing legal framework for off-label drug promotion. Further, until a viable solution is implemented, courts should defer to the government based on a balancing of the parties' respective interests with respect to public health and safety.

CONCLUSION

It is clear that the “false or misleading” threshold is problematic, and simply applying the First Amendment alone is not a sufficient solution. Therefore, developing a non-governmental agency as an intermediary is necessary to resolve the conflicting interests of the FDA and pharmaceutical companies; the First Amendment payoff: If this entity comes into being and is set in place, a validation of a use by that entity should suffice to shut down the government’s false or misleading argument. Until then, if the court must choose between the FDA or pharmaceutical companies, the court should go against the drug companies because of the serious public harm that will likely result from giving pharmaceutical companies the ability to freely promote off-label uses. However, neither of these options, all for one or all for the other outcomes, is desirable or ideal, due to the problems that come with giving total deference to the FDA. The inadequacy of these options establishes the value of my proposal: Drug companies or the legislature should establish a viable independent agency to assess the effectiveness of new uses and the accuracy of off-label promotion.

The importance of the FDA’s regulatory program with respect to off-label drug promotion cannot be overstated. The possible harm that could result from inadequate and misleading off-label marketing is broad in scope and potentially life-threatening to consumers, which is why there is a need to regulate off-label promotion to some extent, in order to hold drug manufacturers responsible for ensuring their statements regarding off-label uses are truthful and non-misleading. At the same time, both individuals and society as a whole view First Amendment protection of free speech as sacrosanct, and the right to be fully informed and the right to inform others is a fundamental protection guaranteed by the First Amendment. However, placing greater value on free speech in order to safeguard First Amendment guarantees also results in potential harm to the public. Financial incentives may encourage drug companies to engage in less rigorous testing for the effectiveness of new uses and promote

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inaccurate or misleading statements regarding off-label use. The conflicting interests of the FDA and drug manufacturers reflects the need to establish a new agency to assess off-label uses and promotions, or at the very least, reform the FDA's regulatory scheme to resolve these problems.