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The FDA Prior-Approval System, Off-Label Promotion and Public Health

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I. Introduction

After decades of near total deference to Agency discretion, in *United States v. Caronia*, the U.S. Court of Appeals for the 2nd Circuit applied first amendment doctrine and concluded that the Food and Drug Administration's (FDA) regulation of off-label promotion of approved drug products unconstitutionally restricted pharmaceutical manufacturers' freedom of speech.¹ The court got it wrong. Regulation of off-label promotion by drug manufacturers is essential to maintaining the effectiveness of the prior-approval drug regulatory system which is the backbone of FDA's ability to protect the public, incentivize research, and provide the public with science based, accurate, and reliable information. Pharmaceutical companies should be prohibited from promoting off-label claims. Restriction of off-label promotion comports with congressional intent, FDA mission, and sound public health policy. Despite recent judicial activism, this enforcement tool should not be diluted.

Nonetheless, there are potentially significant reasons to consider allowing manufacturers to engage in off-label promotion. Physician prescribing of off-label uses is common practice, is not illegal, and is necessary to meet the standard of care in certain therapeutic areas. In addition, Medicare allows reimbursement for essential uses of drugs which are off-label as long as they have been published in official compendia, even though they have not been approved through the NDA process.² So, when an off-label use has been so established as to become the standard of care, why shouldn't pharmaceutical companies be allowed to promote it? It is undeniable that pharmaceutical manufacturers have a First Amendment protected right to freedom of speech but public health policy requires that we override that right to ensure the greater good of protecting the health and safety of the public.

¹ *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012).

² 42 U.S.C. § 1396(r) – 8(k)(6).

This article explores statutory construction, legislative intent, case law, and public health policy in concluding that the answer to the dilemma of off-label promotion is not to reverse course and provide what essentially amounts to an exclusion for pharmaceutical manufacturers from the requirement to prove safety and efficacy of drugs prior to marketing. The answer is for manufacturers to embrace options the Federal Food, Drug and Cosmetic Act (FDCA) and FDA Guidance already provide for relying on less than usual access to clinical data or detailed study reports, or on studies with alternative, less intensive quality control/on-site monitoring, to gain approval for off-label uses. This will advance greater visibility of the use and provide objective, science-based, reliable information to doctors and patients at point of use in the approved labeling where it will do most good.

II. The Prior-Approval Drug Regulatory System

In 1930 Congress created the FDA and authorized them to enforce the Pure Food and Drugs Act of 1906.³ Prior to this enabling Act there was minimal regulation of the pharmaceutical industry and no requirement for determining the safety or efficacy of drug products before introducing them into interstate commerce.⁴ Consequently, the market was flooded with “snake oils” which at best perpetrated fraud on the public and at worst caused serious adverse events and death.⁵ It wasn’t until the “Elixir of Sulfanilamide” poisonings of 1937 which killed 107 people, many of them children, from use of a cough syrup formulated with a deadly industrial solvent, that safety standards were adopted for all human drugs.⁶ This tragedy prompted the passage of the FDCA of 1938 requiring safety testing of all human drugs

³ Brochure: The History of Drug Regulation in the United States; <http://www.fda.gov/AboutFDA/WhatWeDo/History/FOrgsHistory/CDER/CenterforDrugEvaluationandResearchBrochureandChronology/ucm114470.htm>.

⁴ “Milestones in Food and Drug Law History” <http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm>.

⁵ Id.

⁶ Id.

prior to marketing.⁷ While a step in the right direction, the near approval of thalidomide (which caused birth defects in thousands of children in Germany and England) in the U.S. led to the enactment of the 1962 amendments which strengthened the safety requirements and added the requirement for efficacy testing before marketing.⁸

Pursuant to the FDCA, the FDA devised and implemented a system designed to ensure drugs are proven safe and effective before being put into interstate commerce.⁹ The backbone of the prior-approval system of drug regulation is the Investigational New Drug (IND) and New Drug Application (NDA) regulations which require that pharmaceutical manufacturing companies establish the safety and efficacy of new drug products through a rigorous program of *in-vitro*, pre-clinical *in-vivo* (animal), and clinical (human) studies.^{10,11} These include toxicology, pharmacology, and drug-drug interaction studies, for example, to establish the risk-benefit profile of a drug product for its intended use.¹² The IND/NDA process facilitates the early identification of drugs that aren't safe and effective and ensures that they do not get to market. For example, in 2003, Glaxo-Smithkline halted a clinical trial on the safety and efficacy of long acting beta agonists because a statistically significant number of patients on the drug died from asthma related deaths.¹³

The FDCA prohibits manufacturers from marketing drugs which have not been deemed safe and effective through the NDA prior-approval process.¹⁴ Pursuant to the FDCA, to support

⁷ *Id.*

⁸ *Id.*

⁹ 21 CFR § 312; 21 CFR § 314.

¹⁰ *Id.*, Federal Food, Drug, and Cosmetic Act § 505 (21 U.S.C. § 355).

¹¹ *Id.*

¹² *Id.*

¹³ United States 'Complaint at 44, United States v. GlaxoSmithKline, no. 11-10398-RWZ (D. Mass. Oct.26, 2011).

¹⁴ Federal Food, Drug, and Cosmetic Act §§ 301(d), 505(a) [21 U.S. .C . §§ 331(d), 355(a)].

approval, an NDA must include “adequate data and information on the drug’s safety” and “substantial evidence of effectiveness.”¹⁵ The FDCA mandates the submission of full reports of investigations to meet these requirements. Depending on the type of data however, a manufacturer may chose to file their request for approval of a new drug under either a 505(b)(1) application or a 505(b)(2) application.¹⁶ A 505(b)(1) application includes full reports of investigations sponsored by the applicant along with the actual data supporting safety and effectiveness.¹⁷ A 505(b)(2) application includes full reports of investigations that are not sponsored by the applicant but are provided by reference to data generated by someone else.¹⁸ For example, published literature reports may be used in a 505(b)(2) application to support safety and efficacy.¹⁹

An applicant may also gain approval for a new indication, or different manner of use, for an already approved drug product through the Supplemental New Drug Application (SNDA) process.²⁰ Much of the data supporting approval of a SNDA may be included by reference to the data submitted in the original NDA and only data and information about the new indication or manner of use need be generated and included.²¹

When approval for a new indication or different manner of use for an already approved drug product is not sought, information about those potentially beneficial uses is disseminated to the medical community by inclusion in compendia, journal articles, and textbooks.²² These uses

¹⁵ Id.

¹⁶ Federal Food, Drug, and Cosmetic Act §505(b)(1) [21 U.S.C § 505(b)(1)].

¹⁷ Id.

¹⁸ Federal Food, Drug, and Cosmetic Act §505(b)(2) [21 U.S.C § 505(b)(2)].

¹⁹ Id.

²⁰ 21 C.F.R. § 314.70

²¹ Id.

²² “Speeches by FDA Officials” Linda A. Suydam, D.P.A., FDLI Conference Keynote Address, Sept.13, 1999. <http://www.fda.gov/NewsEvents/Speeches/SpeechArchives/ucm054540.htm>

are also disseminated via discussion at independent symposia, educational sessions, and professional meetings.²³ Finally, knowledge about these uses is spread by off-label promotion.²⁴ It has been suggested that dissemination via compendia, journal articles, textbooks independent symposia, educational sessions, and professional meetings are better than relying on manufacturer's off-label promotion for a variety of reasons and FDA in fact prohibits dissemination by off-label promotion.²⁵ Post NDA approval, advertising and promotion of an approved drug product for a use that is not identical to that in an effective (i.e. approved) NDA undermines the prior-approval drug regulatory scheme because the safety and efficacy of the off-label use has not been established through the rigorous process established by the FDA pursuant to the FDCA.

Recognizing the need for oversight of manufacturers' off-label promotion activities, Congress amended the FDCA Act in 1962 and gave FDA the authority to regulate the advertising and promotion of prescription drug products as well.²⁶ This was a response, in part, to Congressional concerns that doctors could not adequately evaluate frequently misleading claims by drug manufacturers without a body of objective, reliable information.²⁷ Pursuant to this authority, FDA provided criteria for appropriate advertising and promotion and prohibited the advertising and promotion of drugs for any use other than that subject to an effective NDA.²⁸

²³ Id.

²⁴ Id.

²⁵ Guidance for Industry: Responding to Unsolicited requests for Off-Label Information about Prescription Drugs and Medical Devices; Draft 2011 at 2.

²⁶ "Milestones in Food and Drug Law History"

<http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm>.

²⁷ "Speeches by FDA Officials" Linda A. Suydam, D.P.A.,FDLI Conference Keynote Address, Sept.13, 1999.

<http://www.fda.gov/NewsEvents/Speeches/SpeechArchives/ucm054540.htm>.

²⁸ 21 CFR § 201, 21 CFR § 202.

Advertising violates the FDCA if it is false or misleading, fails to provide fair balance, and/or fails to reveal material facts.²⁹

Off-label promotion is the promotion of a drug for a use or uses that have not been approved by the FDA as safe and effective. These may include, for example, claims for the use of a drug to treat a different condition, to treat a different population of patients, or to be used according to a different dosing regimen. To ensure successful patient outcomes, advertising and promotional material must accurately state what condition the drug is approved for and how to use it correctly. The safety and efficacy of use for any other condition or in any other way is unknown and puts the public at risk.

FDA's mission is not limited to protecting the public health by assuring the safety and efficacy of drugs.³⁰ It is also to advance the public health by speeding innovations that make medicines more effective, safer, and more affordable.³¹ Moreover, it aims to help the public obtain accurate, science-based information they need to use drugs effectively.³² Prohibiting drug manufacturers' off-label promotion is essential to achieving each of these three goals. It ensures the integrity and effectiveness of the prior-approval drug regulatory system which is the backbone of the FDA's ability to protect the public by keeping unsafe and ineffective drugs off the market; advances the public health by incentivizing the generation of accurate science-based information on safety and efficacy, and helps patients get the accurate, science-based information they need to use drugs to maintain and improve their health.³³

²⁹ Id.

³⁰ Statement of FDA Mission; <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM298331.pdf>.

³¹ Id.

³² Id.

³³ "Speeches by FDA Officials" Linda A. Suydam, D.P.A., FDLI Conference Keynote Address, Sept.13, 1999. <http://www.fda.gov/NewsEvents/Speeches/SpeechArchives/ucm054540.htm>

III. Public Health Policy

Public health policy suggests that off-label promotion be regulated to ensure viability of the prior-approval drug regulatory system. When the prior-approval drug regulatory system is circumvented and manufacturers are allowed to advertise and promote at will, human tragedy often ensues. Based on the amount of money the pharmaceutical industry expends on promotion and advertising, it's undisputed that promotion and advertising are extremely effective vehicles for increasing the use of drug products.³⁴

The global tobacco epidemic is a direct result of circumventing the prior-approval drug regulatory system and allowing advertising and promotion to go unregulated. Based on the FDCA, the FDA defines the term “drug” as articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and articles intended to affect the structure or function of the body. It defines “new drugs” as any drug not generally recognized among qualified experts as safe and effective and subjects them to the prior-approval requirements of the FDCA.³⁵ Even though Tobacco companies strategically don't make drug claims for their products today, they have long touted a variety of health claims and disease states treated by smoking. Early ads included claims for weight loss (“To Keep a Slender Figure”), as well as asthma and other diseases of the mouth, throat, and lungs (Dr. Batty's).^{36,37} Many ads indirectly promoted the benefits of smoking by featuring doctors (“More Doctors Smoke Camels”).³⁸

³⁴Big Pharma Spends More On Advertising Than Research And Development, Study Finds, Jan.7, 2008 <http://www.sciencedaily.com/releases/2008/01/080105140107.htm>.

³⁵ 21 U.S.C § 201(g)(1)

³⁶ “When smoking was good for you! Advertisers used to claim cigarettes would keep women slim and beautiful”; <http://www.dailymail.co.uk/news/article-2107969/When-smoking-good-Advertisers-used-claim-cigarettes-women-slim.html#ixzz2QU21DZmJ>

³⁷Advertisement: “Dr. Batty's For Your Health Asthma Cigarettes”

³⁸ Advertisement: “More Doctors Smoke Camels”

Furthermore, it is uncontroverted that tobacco products affect the structure or function of the body.³⁹ Thus, tobacco products should have fallen under the rubric of the FDCA of 1938. Even though the Court in *Brown & Williamson* concluded that tobacco is not a drug, and thus not subject to the FDCA, Congress subsequently passed the Family Smoking Prevention and Tobacco Control Act (TCA) granting FDA the authority to regulate tobacco products.^{40,41} This authority covers the content, marketing and sale of tobacco products and requires manufacturers to seek approval for any new tobacco products.⁴² From that standpoint, the TCA is remarkably similar in scope to the FDCA. Global consumption of cigarettes has risen steadily since they were introduced at the beginning of the 20th Century.⁴³ Scientific evidence has shown that all forms of tobacco cause health problems which frequently result in death or disability and no other consumer product is as dangerous or deadly.⁴⁴ The global tobacco epidemic is a clear example of the result that ensues when the prior-approval drug regulatory system is circumvented and advertising and promotion goes unregulated. Had Congress and the Courts accepted tobacco products as drugs and subjected them to FDA regulation sooner, this massive public health tragedy would have been averted because tobacco product manufacturers would have had to provide adequate data and information on their products' safety. This data readily would have revealed the dangerous side effects from use of tobacco products and led to their prohibition.

³⁹ Knut-Olaf Haustein, Tobacco or Health?: Physiological and Social Damages Caused by Tobacco Smoking; (Springer-Verlag Berlin Heidelberg New York) 2001.

⁴⁰ FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120 (2000).

⁴¹ P.L. 111-31 (2009); 21 U.S.C. 301.

⁴² Id.

⁴³ Dr. Judith Mackay, Dr. Mihael Eriksen, The Tobacco Atlas (World Health Organization) 2002.

⁴⁴ Id.

A number of other off-label drug uses have resulted in tragic consequences from circumventing the prior-approval drug regulatory system.⁴⁵ These include off-label use of drugs to treat AIDS, life threatening arrhythmias, angina and hypertension, and post operative pain.⁴⁶

In a desperate attempt to stem the AIDS epidemic, the drug ddC was manufactured, sold and used before clinical trials were conducted to assess its safety and efficacy. The studies revealed that those using ddC as initial therapy had a death rate at least twice as high as patients on AZT, the drug already approved for the treatment of AIDS.⁴⁷

In another example, the drugs encainide and flecainide were used off-label to prevent increased mortality of heart attack victims who had high levels of ventricular premature complexes.⁴⁸ Although the use was unstudied and unapproved it was supported in some published peer-reviewed journal articles.⁴⁹ When the value of this therapy began to be suspected, the National Institutes of Health conducted clinical studies and discovered that the death rate of patients on the combination was more than twice the rate of patients on placebo.⁵⁰

Another example includes the widespread off-label use of calcium channel blockers, instead of beta blockers, in post-heart attack patients which was fostered by publications that could be interpreted as supportive.⁵¹ Instead of helping, this off-label use likely cost thousands of lives each year.⁵²

⁴⁵ "Speeches by FDA Officials" Linda A. Suydam, D.P.A., FDLI Conference Keynote Address, Sept.13, 1999. <http://www.fda.gov/NewsEvents/Speeches/SpeechArchives/ucm054540.htm>.

⁴⁶ Id.

⁴⁷ Id.

⁴⁸ Id.

⁴⁹ Id.

⁵⁰ Id.

⁵¹ "Speeches by FDA Officials" Linda A. Suydam, D.P.A., FDLI Conference Keynote Address, Sept.13, 1999. <http://www.fda.gov/NewsEvents/Speeches/SpeechArchives/ucm054540.htm>.

⁵² Id.

A final example is the risk of serious, life-threatening, respiratory depression associated with the off-label use of the fentanyl patch for post-operative pain which was based on a number of publications describing the patch as safe and effective for that use.⁵³ Without a comprehensive review of these publications and any other data available, it is unclear whether these publications would have been adequate in terms of quantity and quality to support FDA approval of this indication. For sure though, we would know the answer to that question had the manufacturer collected the data available and submitted it to the FDA for review. Without this no one would be able to say how much more data, if any, would be needed to support or dispute the safety and efficacy of this off-label use.

In sum, protection of off-label promotion as a first amendment right circumvents the NDA prior-approval process and exposes patients to treatments which have not been vetted through the NDA prior-approval process. This brings us full circle back to pre-1906 when drugs were considered commodities and sold as any other commercial good. History has shown this results in human tragedy. These tragedies trumpet that from a public policy standpoint, society's right to freedom from unsafe or ineffective drugs must trump manufacturer's right to free speech.

IV. Freedom of Speech

In *United States v. Caronia*, a sales representative responsible for detailing the drug Xyrem[®] to physicians for cataplexy (weak or paralyzed muscles caused by narcolepsy) promoted the drug for insomnia, fibromyalgia, restless leg syndrome, Parkinson's disease and Multiple Sclerosis as well.⁵⁴ The FDA charged Caronia with intent to introduce a misbranded drug into interstate commerce (because it lacked adequate directions for its off-label intended use) but the

⁵³ *Id.*

⁵⁴ *United States v. Caronia*, 703 F.3d 149 (2d Cir.2012)

court decided he was being prosecuted for his speech in violation of the First Amendment and applied First Amendment doctrine instead.⁵⁵

A. First Amendment Doctrine & Caronia Analysis

The First Amendment of the U.S. Constitution prohibits Congress from making any law that abridges the freedom of speech.⁵⁶ While bribery, perjury, and anti-trust conspiracies are not protected, and political speech is well protected, commercial speech has historically been less protected allowing some restrictions to be deemed constitutional.⁵⁷ It was not until *Central Hudson* was decided in 1980 that commercial speech first received First Amendment protection.⁵⁸ In *Central Hudson*, commercial speech was analyzed under a heightened scrutiny standard.⁵⁹ Subsequent to *Central Hudson*, in 1985, *Zauderer* was decided which provides for some types of commercial speech to be analyzed pursuant to a normal scrutiny standard.⁶⁰

Under normal scrutiny, the *Zauderer* Test (rational basis) is applied.⁶¹ To survive a constitutional challenge under *Zauderer*, the speech must be purely factual and uncontroversial, reasonably related to the State's interest in preventing deception, and not unjustified or unduly burdensome.⁶² *Zauderer* applies to speech which the government forces a company to make in order to prevent deception as is the case with certain required warnings and disclosures.⁶³ The Court in *Caronia* did not apply *Zauderer* because the speech restricted was voluntary commercial

⁵⁵ Id.

⁵⁶ U.S. Const. amend. I.

⁵⁷ Ralph F. Hall, *FDA, Caronia and the 1st Amendment*, FDLI Annual Conference 2013; http://www.fdpi.org/docs/default-document-library/hall_2013new.pdf?sfvrsn=0.

⁵⁸ *Cent. Hudson*, 477 U.S. 557.

⁵⁹ Id.

⁶⁰ *Zauderer v. Office of Disciplinary Counsel of Sup. Ct. of Ohio*, 471 U.S. 626.

⁶¹ *R.J. Reynolds v. FDA*, 696 F.3d 1205 (D.C. Cir. 2012).

⁶² Id.

⁶³ Id.

speech. One could well posit that the failure to include adequate directions for its off-label intended use amounted to the failure to make a disclosure compelled by law and thus apply *Zauderer* but the Court did not do so in this case.⁶⁴

Under heightened scrutiny, either the Central Hudson Test or the Strict Scrutiny Test is applied.⁶⁵ Pursuant to *Central Hudson*, to determine if the speech deserves protection, the speech must not be misleading or about an illegal activity, and the government must prove that its asserted interest is substantial, the restriction directly and materially advances the states' interest, and the restriction is narrowly tailored.⁶⁶ To survive a constitutional challenge under Strict Scrutiny, the government must prove that their interest is compelling, the restricted speech is vital to advancing their interest, and the restriction is narrowly tailored.⁶⁷ Voluntary commercial speech is typically analyzed under heightened scrutiny.⁶⁸

In analyzing Caronia, the Court followed the First Amendment analysis and decision in *Sorrell v. IMS Health*.⁶⁹ In *Sorrell*, the U.S. Supreme Court decided that speech in aid of pharmaceutical marketing is a form of free expression protected by the First Amendment.⁷⁰ *Sorrell* stands for the premise that a law which imposes a restriction on content and speaker based speech that is subject to heightened scrutiny is presumed invalid unless it is justified in light of a substantial government interest.⁷¹ The Caronia panel found the speech was content based because it permitted on-label promotion but prohibited off-label promotion, and speaker

⁶⁴ Frank Pasquale, Seton Hall Law AWR Comments, Spring 2013.

⁶⁵ Kathleen M. Sullivan, Gerald Gunther, Constitutional Law (Foundation Press) 2010.

⁶⁶ *Id.*

⁶⁷ *Id.*

⁶⁸ *Id.*

⁶⁹ *Sorrell v IMS Health, Inc.*, 131 S.Ct.2653 (2011).

⁷⁰ *Id.*

⁷¹ *Id.*

based because it applied only to pharmaceutical companies and not to doctors or anyone else.⁷² Because the restricted speech was voluntary commercial speech the Court applied heightened scrutiny. Using the Central Hudson test, they found that the restriction did not meet the third (the restriction must advance a substantial government interest) or fourth prong (the restriction must be narrowly tailored) and concluded that FDA's restriction of pharmaceutical manufacturers' off-label promotion speech was unconstitutional in violation of the First Amendment.⁷³ Paramount to this finding, however, is the assumption made by the court a priori that the speech was truthful.

B. The Sorrell Analysis

Before getting to the Sorrell analysis, it's important to note, that the Court in Caronia did not address certain critical issues before applying First Amendment doctrine. First, the court decided that Caronia was prosecuted for his speech, but the charge was misbranding, and his speech was only used as evidence to prove misbranding (intent to ship a misbranded drug in interstate commerce.)⁷⁴ Under the FDCA, a drug is misbranded if it lacks adequate directions for lay use.⁷⁵ By definition, the legal status of a drug is "over-the-counter" unless it is impossible for adequate directions for lay use to be created.⁷⁶ When it is impossible to create adequate directions for lay use, the legal status is "prescription" and it is exempted from the requirements for adequate directions as long as the intended use is the same as that approved in an NDA.⁷⁷

⁷² United States v. Caronia, 703 F.3d 149 (2d Cir.2012).

⁷³ Id.

⁷⁴ Id, Dissent at 172.

⁷⁵ 21 C.F.R. § 352.

⁷⁶ Federal Food, Drug, and Cosmetic Act § 503(b)(1) [21 USC § 353(b)(1)].

⁷⁷ Id.

Thus, a drug is misbranded if it is labeled, advertised, or promoted for a use that is not the same as the labeling in the approved NDA.⁷⁸

In *Sorrell*, Vermont's Prescription Confidentiality Law was challenged and found to have unconstitutionally burdened the speech of pharmaceutical marketers and data miners without adequate justification.⁷⁹ With the goal of protecting patient privacy, this law prohibited pharmaceutical manufacturers from using prescriber-identifying information for marketing purposes.⁸⁰ In *Sorrell* the law was discriminatory because it only restricted manufacturers' use of the data while others were allowed to use the data even though they too could compromise patient privacy.⁸¹

Sorrell is distinguishable from *Caronia* because in *Sorrell*, the VT law that restricted use of prescriber-identifiable data in promotional activities by pharmaceutical manufacturers targeted speech directly.⁸² In *Caronia*, the conviction was based on the use of speech as evidence to prove intended use which does not even implicate the First Amendment. Thus, First Amendment doctrine should not have been applied at all.⁸³

The *Caronia* Panel also based its conclusion on a characterization of the restricted speech as speaker and content based.⁸⁴ The speech, however, was not content based because off-label

⁷⁸ Pursuant to section 503(b)(1) of the Act, [21 U.S.C. § 353(b)(1)], a prescription drug is not safe for use except under the supervision of a practitioner licensed by law to administer such drug. By definition, a prescription drug's directions for use are not adequate to enable a layperson to safely use the drug for its intended uses. See 21 C.F.R. § 201.5. Consequently, failing to bear adequate directions for use pursuant to section 502(f)(1) of the Act, [21 U.S.C. § 352(f)(1)] and lacking an approved application, the drug not exempt from 21 C. F.R. § 201.115 and is therefore misbranded.

⁷⁹ *Sorrell v IMS Health, Inc.*, 131 S.Ct.2653 (2011).

⁸⁰ *Id.*

⁸¹ *Id.*

⁸² *Id.*

⁸³ *United States v. Caronia*, 703 F.3d 149 (2d Cir.2012).

⁸⁴ *Id.*

promotion is restricted for all drugs, not just particular drugs, and it was not speaker based because off-label promotion is restricted for all manufacturers, not just particular manufacturers. Pharmaceutical manufacturers are the only actors that FDA regulates so it's incorrect to conclude that they were discriminated against while doctors were not because doctors aren't in the universe of actors regulated by FDA.

Nonetheless, pursuant to the *Sorrell* analysis, the court concluded that the law restricting off-label was presumptively invalid and it looked to the Central Hudson Test to determine if was justified in light of the government interest involved.⁸⁵ Pursuant to *Caronia*, the test for justifying the restriction of commercial speech in the food and drug law realm now appears to be a sequential Sorrell – Central Hudson Test.

C. The Central Hudson Test Analysis

Under the Central Hudson test, to be protected, the speech must be truthful, not misleading, and not about an illegal activity. If the speech is protected, a restriction is justified only if it supports a substantial government interest, directly advances that interest to a material degree, and is narrowly drawn and not more extensive than needed.⁸⁶

1. The First Prong

Applying the first prong of the Central Hudson Test we find there is no question that the activity promoted, off-label drug *use*, is not illegal (doctors can prescribe off-label uses of drugs for patients under their care and patients can use drugs off-label). Off-label *promotion*, however, is inherently misleading. Off-label promotion implies that a drug is safe and effective for a

⁸⁵ *Id.*

⁸⁶ *Cent. Hudson*, 477 U.S. 557.

particular use when the pharmaceutical manufacturer doesn't really know. While the promotional information may be true, and the use truly safe and effective, by statutory definition, the speech is misleading because the use hasn't been proven safe and effective according to the criteria set out in the FDCA. Thus, doctors may be relying on misleading information when they conclude that an off-label use is safe and effective enough to prescribe to their patients. Pursuant to the statute, safe and effective means that 1) the use is subject to an effective NDA; 2) the NDA includes full reports of investigations containing "adequate data and information" on the drug's safety and "substantial evidence" of effectiveness (for that use), 3) the data and information was assessed by experts qualified by scientific training and experience to evaluate the safety and effectiveness of the drug for use under the conditions prescribed, recommended, or suggested, 4) the benefit of the drug use was determined to be greater than the risk, and 5) labeling is available (for that use) which is "adequate" to explain what the drug is intended for and the risks and benefits of using it for that condition.⁸⁷ Thus, for an off-label use, where the manufacturer hasn't meet the statutory requirements for deeming it safe and effective, the speech is inherently misleading and it must fail the first prong of the Central Hudson Test. This means that the speech is not protected under the Constitution and the government can restrict it without scrutiny. Congress expressly defined safety and effectiveness in the FDCA.⁸⁸ They recognized that no drug is ever one hundred percent safe and effective, and thus set the standard for safety and effectiveness based on scientific evidence. Had Congress wanted to leave the standard for determining the safety and efficacy of drugs up to manufacturers, they would not have expressly defined it, and would not have authorized FDA to enforce it.

⁸⁷ Federal Food, Drug, and Cosmetic Act § 505 (21 U.S.C. § 355).

⁸⁸ Federal Food, Drug, and Cosmetic Act § 505 (21 U.S.C. § 355).

Nonetheless, the court in *Caronia* assumed the speech was truthful (in part, because the government did not make the assertion that it was not.)⁸⁹ The Court stated that, prohibiting off-label promotion “paternalistically interferes with the ability of physicians and patients to receive potentially relevant treatment information” and thereby “could inhibit, to the public’s detriment, informed and intelligent treatment decisions.”⁹⁰ To the contrary, banning off-label promotion prevents doctors and patients from being misled with potentially false information. The court also claimed that the FDCA contemplated off-label drug *use*.⁹¹ This may be true but the FDCA most likely did not contemplate off-label *promotion*, or that manufacturers would circumvent the system by promoting off-label uses without going through the approval system. It’s fair to say that Congress presupposed that manufacturers would follow the process lest they wouldn’t have legislated it and authorized FDA to enforce it.

2. The Second Prong

The government’s substantial interest in prohibiting off-label promotion is self-evident and the Court easily established that the second prong was satisfied. They found the government did have a substantial interest in “preserving the effectiveness and integrity of the FDCA’s drug approval process, and an interest in reducing patient exposure to unsafe and ineffective drugs.”⁹²

3. The Third Prong

Pursuant to the third prong of the *Central Hudson* test, the government may restrict speech if it directly advances their substantial interest to a material degree.⁹³ The FDA has a

⁸⁹ *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012).

⁹⁰ *Id.*

⁹¹ *Id.*

⁹² *Id.*

⁹³ *Cent. Hudson*, 477 U.S. 557.

substantial interest in banning off-label promotion to achieve its tri-fold objectives: protect the public from harm from unsafe and ineffective drugs, advance the public health by supporting innovations that make medicines more effective, safer, and affordable, and help the public get accurate, science based information needed to use drugs successfully. Banning off-label promotion directly advances the Government's interest in a material way because off-label promotion circumvents the prior-approval drug regulatory system which thereby 1) exposes patients to risk of harm from unsafe and ineffective drugs because FDA is robbed of the opportunity to keep unsafe drugs off the market; 2) suppresses innovation by allowing manufacturers to market drugs without first proving safety and efficacy thereby muting the incentive to generate accurate science based information and 3) prevents the public from getting accurate, science base information because none will be generated.⁹⁴ Without needing to file an NDA, manufacturers have no incentive to conduct innovative research. Without conducting research, manufacturers don't have the information necessary for an adequate assessment of the drug's safety and efficacy for the promoted off-label use. Without an objective assessment by qualified experts, the information provided by manufacturers cannot be complete, unbiased or reliable. Incomplete and biased information is inherently false and misleading. Without consequences for false and misleading promotion, companies have no incentive to conduct studies or collect otherwise available data and information (e.g. published literature), to submit to FDA to definitively establish the safety and efficacy an off-label use.

To legally establish the safety and effectiveness of an off-label use, manufacturers must meet the FDCA definition of substantial evidence which FDA has clearly interpreted and

⁹⁴ "Speeches by FDA Officials" Linda A. Suydam, D.P.A., FDLI Conference Keynote Address, Sept.13, 1999. <http://www.fda.gov/NewsEvents/Speeches/SpeechArchives/ucm054540.htm>.

described in numerous regulation and guidance.^{95,96} Substantial evidence typically requires full investigations including two adequate and well controlled studies but in certain circumstances less evidence is acceptable.⁹⁷ Without generating substantial evidence, manufacturers advance their own interests over that of the public. Off-label promoters have an inherent conflict of interest as their primary interest is investor return. Conducting full investigations of off-label uses is not in drug manufacturers' best interest. To conduct these investigations, resources need to be diverted from the study of other drugs. Diverting these resources is not justified when there are no consequences for promoting and selling a drug for an off-label use without generating the data. Even worse, the studies may fail thus cutting off an otherwise available revenue stream. Likewise, compiling and assessing a comprehensive review of all of the data and information otherwise unimpeded (i.e. published literature) about an off-label use is also not in the company's best interest. Again, the assessment may reveal the drug is not safe or not effective. When pharmaceutical manufacturers can bypass the system and financially gain from off-label uses without doing the research, the cost and risk of doing research can't be justified from a business perspective.

If there were consequences for false and misleading promotion, drug manufacturers would conduct the studies or assessments needed. Positive results from these studies and assessments would support approvals through the NDA system while negative results would prevent promotion of those uses. In this way, and doctors and patients would get accurate science based information and patients would be protected from using drugs in ways that have not been shown to be safe and effective.

⁹⁵ 21 C.F.R. § 314

⁹⁶ FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biologic, May 1998.

⁹⁷ Id.

Nonetheless, the Court in *Caronia* found the restricted speech did not meet the third prong because it did not directly advance the government’s interest to a material degree.⁹⁸ The court reasoned that because off-label use *is* allowed and the speech is truthful prohibiting manufacturers from promoting them doesn’t undermine the drug approval process nor help reduce exposure to unsafe and ineffective drugs.⁹⁹ Had the truthfulness of off-label promotion been assessed in *Caronia*, the Court well may have found that off-label speech is not protected.

In addition, the court said “criminalizing manufacturers’ promotion of off-label use while permitting others to promote such uses to doctors is an indirect and questionable effective means to achieve the goal of shepherding physicians to prescribe drugs only on-label.”¹⁰⁰ The court clearly misunderstands FDA’s goal in restricting off-label promotion. “Shepherding physicians to prescribe drugs only on-label” is not only not the objective, it’s contrary to FDA’s goal. FDA’s goal is to safeguarding the public, advancing the public health by encouraging innovation in medicine, and disseminating truthful information to patients. Understanding the goal is paramount to determining whether the means to achieve that goal is appropriate. Had the Court recognized the correct goal, they likely would have found the means acceptable.

4. The Fourth Prong

To meet the fourth prong of *Central Hudson*, the restriction cannot be more extensive than needed to advance the government policy.¹⁰¹ Banning of off-label promotion by manufacturers is not more extensive than needed because drug manufacturers are the only group restricted. Banning off-label speech across the board would be over inclusive, limit the free

⁹⁸ *United States v. Caronia*, 703 F.3d 149 (2d Cir.2012).

⁹⁹ *Id.*

¹⁰⁰ *Id.*

¹⁰¹ *Cent. Hudson*, 477 U.S. 557.

exchange of information between doctors and educational institutions, and be a disservice to patients.¹⁰² Limiting the ban to drug manufacturers specifically targets the single group that has inordinate incentives for distortion if they don't participate in it.¹⁰³ FDA doesn't regulate doctors or the public, they only regulate drug manufacturers.¹⁰⁴ In addition, the regulations don't discriminate among manufacturers (i.e. all manufacturers are banned alike). *Sorrell* is distinguishable because the law did not discriminate within the regulated universe of actors.¹⁰⁵ Even the court in *Sorrell* conceded that "the first amendment does not prevent restrictions directed at commerce or conduct from imposing incidental burdens on speech".¹⁰⁶

The Caronia Court speculated that there are numerous less restrictive means available to meet the government's goal.¹⁰⁷ They suggested that if FDA is concerned that physicians may be deceived by off-label promotion, the agency "could guide physicians and patients in differentiating between misleading and false promotion, exaggerations and embellishments, and truthful or non-misleading information."¹⁰⁸ Given FDA's resource constraints, it's highly unlikely that this suggestion would be feasible, or effective.¹⁰⁹ The Court rejected FDA's defense that this and other means were not administrable, feasible, or effective and said that FDA must prove that they aren't practical, effective, or feasible.¹¹⁰ Hasn't history already proven this? The sulfanilamide and thalidomide tragedies and the global tobacco epidemic alone support the fact

¹⁰² United States v. Caronia, 703 F.3d 149 (2d Cir.2012); Dissent.

¹⁰³ Id.

¹⁰⁴ "Speeches by FDA Officials" Linda A. Suydam, D.P.A., FDLI Conference Keynote Address, Sept.13, 1999.

<http://www.fda.gov/NewsEvents/Speeches/SpeechArchives/ucm054540.htm>.

¹⁰⁵ See discussion supra Part IV. B.

¹⁰⁶ *Sorrell v IMS Health, Inc.*, 131 S.Ct.2653 (2011).

¹⁰⁷ United States v. Caronia, 703 F.3d 149 (2d Cir.2012).

¹⁰⁸ Id.

¹⁰⁹ Efthimios Parasidis, Patients Over Politics: Addressing Legislative Failure in the Regulation of Medical Products, 2011 Wis. L. Rev. 929.

¹¹⁰ United States v. Caronia, 703 F.3d 149 (2d Cir.2012).

that allowing circumvention of the prior-approval drug regulatory system and unregulated drug advertising and promotion do not achieve the goal of protecting the public from unsafe and ineffective drugs.¹¹¹ Nonetheless, the Caronia Court found the prohibition of off-label promotion was more extensive than needed.¹¹² Had the Court considered the realities of the FDA's resource limitations and the fact that drug regulation and tragedy are inversely related, they would likely have concluded otherwise.

In sum, it is undisputed that doctors are allowed to prescribe off-label uses under the auspices of the practice of medicine. This allows innovative medicine to quickly get to patients that need it without having to wait for full investigations and NDA approval. Awareness of off-label uses is generated not only by off-label promotion but also by compendia, journal articles, textbooks, independent symposia, professional meetings.¹¹³ Pharmaceutical manufacturers contend that allowing off-label promotion serves doctors and their patients, and that government regulation should not impede the practice of medicine by restricting off-label promotion. Despite this noble endeavor pharmaceutical manufacturers have a conflict of interest. It is not FDA's goal to prevent ill patients' access to drugs¹¹⁴. FDA's goal is to get objective, science-based, and reliable information about drugs to ill patients so they can use them successfully.¹¹⁵ Thus, despite the fact that First Amendment doctrine should not have been applied to this case at all, the Central Hudson test proves rather than denies that the restriction of off-label promotion is justified whether the speech is considered truthful or not.

¹¹¹ See discussion supra Part III.

¹¹² United States v. Caronia, 703 F.3d 149 (2d Cir.2012).

¹¹³ "Speeches by FDA Officials" Linda A. Suydam, D.P.A.,FDLI Conference Keynote Address, Sept.13, 1999. <http://www.fda.gov/NewsEvents/Speeches/SpeechArchives/ucm054540.htm>.

¹¹⁴ Id.

¹¹⁵ Id.

V. Academia

In a review entitled, “*Off-Label Prescription Advertising, The FDA and the First Amendment: A Study in the Values of Commercial Speech Protection*,” the authors Klasmeier and Redish conclude that FDA is clueless when it comes to the First Amendment and commercial speech rights.¹¹⁶ Klasmeier and Redish, fail to recognize and appreciate the position that the FDA is in. The FDCA and FDA’s mission require that FDA manage a delicate balance between protecting the public *and* enhancing activities that result in scientific findings *and* ensuring these scientific facts are disseminated truthfully, understandably, and without deception to those who need them. These objectives, in tension with each other, require a delicate balance.

Klasmeier and Redish’s claim that, “FDA’s categorical prohibition of off-label use amounts to a classic suppression of commercial speech” may be true but the Supreme Court in *Sorrell* concedes that commercial speech may be restricted.¹¹⁷ Commercial speech is *not* and should not be afforded full protection like these authors promote. The Central Hudson Test provides the framework for the analysis to determine when commercial speech is being unconstitutionally suppressed and when it is not.¹¹⁸ In the context of public health and safety, suppression of off-label promotion is justified pursuant to *Central Hudson*.¹¹⁹

The authors’ contend that “the government cannot suppress communication completely when the danger can be avoided by the provision of more information, rather than less” but they fail to appreciate the fact that neither the FDA nor the manufacturer *has* the information to

¹¹⁶ Coleen Klasmeier, Martin H. Redish, *Off-Label Prescription Advertising, The FDA and the First Amendment: A Study in the Values of Commercial Speech Protection*; American Journal of Law and Medicine 2011.

¹¹⁷ *Sorrell v IMS Health, Inc.*, 131 S.Ct.2653 (2011).

¹¹⁸ *Cent. Hudson*, 477 U.S. 557.

¹¹⁹ See discussion *supra* Part IV.C.

provide.¹²⁰ If the manufacturer had adequate data and information on the safety, and substantial evidence of effectiveness, of the off-label use they would submit it to FDA for review and approval thereby getting the information on the drug label itself. Having the off-label use made on-label is far more valuable to manufacturers because the new use gets much more visibility and eliminates the expense of sales calls. In this way, when truly beneficial, the use is as transparent as the light of day for all doctors to see – it's no longer limited to linear dissemination of the message from the sales rep to doctor 1, then from doctor 1 to doctor 2, etc., which suffers from the problem of gossip distortion as depicted in many comedic sketches of the 20th Century where the message at the end of the phone line is not the same as the message at the beginning. In this context though, distortion of the message is not funny. In other words, getting an off-label use on-label blasts it out of the dark ages into the new millennium of transparency with all the benefits that come along with that, like accuracy, completeness, and reliability of the message.

The authors state that FDA could attempt to redefine its interest more narrowly to finesse the problems under the third and fourth prongs of Central Hudson. Again they fail to recognize that FDA's mission, as directed by Congress, is three fold and narrowing their interest would require Congress to Amend the FDCA.¹²¹

The authors state that it is impossible to assert that the public health and safety will be advanced by the categorical prohibition of off-label promotion because FDA allows off-label *use* yet bans off-label *promotion* which deprives ill patients of valuable and lawful treatments for the

¹²⁰ Coleen Klasmeier, Martin H. Redish, Off-Label Prescription Advertising, The FDA and the First Amendment: A Study in the Values of Commercial Speech Protection; American Journal of Law and Medicine 2011.

¹²¹ Id.

simple reason that their doctors are unaware of their existence.¹²² They suggest that the FDA cure their constitutional speech problem by prohibiting doctors from prescribing off-label use at all so that conduct instead of speech is targeted.¹²³ The authors' logic is flawed and they miss the point of FDA's existence. A ban on off-label prescribing would *completely* deprive ill patients from potentially beneficial treatments whereas banning the promotion of off-label uses only shifts the speech from manufacturers who have inherent bias to independent medical and public health organizations. Again, the authors fail to appreciate the complexity of FDA's mandate: to prevent harm *and* advance health. Without undergoing rigorous scientific analysis and evaluation, even the FDA does not know which claim is truthful and beneficial, and which not, so from a public health standpoint they logically would not prevent the drug's off-label use unless it were definitively proven that it was not truthful, and harmful. Thus, if FDA prevents off-label use, patients will suffer from lack of access to potentially valuable treatments, and if they don't prevent off-label use, patients will suffer from exposure to potentially harmful treatments. Thus, either way you look at it patients suffer. From a public health ethics viewpoint, depriving all ill patients of potentially lifesaving treatments is far worse than depriving pharmaceutical manufacturers additional sales from off-label uses with an incidental burden on their freedom of speech. By not generating the scientific evidence required by law under the FDCA, pharmaceutical manufacturers have effectively forced FDA into the position of having to allow off-label use. The authors claim that FDA is extorting manufacturers into conducting studies when they have "absolutely no legal obligation to undertake such action" but that is absolutely untrue.¹²⁴ They, in fact, absolutely *do* have a legal obligation under the FDCA § 505(a) which states, "no person shall introduce into interstate commerce any new drug unless

¹²² *Id.*

¹²³ *Id.*

¹²⁴ *Id.*

approval of an application filed pursuant to section 505 subsection (b) of (j) is effective.”¹²⁵ The law could not be clearer: before you can market a drug you must gain approval for it through the prior-approval drug regulatory scheme which means you must provide evidence of safety and effectiveness. To the contrary, pharmaceutical manufacturers are using the public health argument to advance their own interest to force the FDA to let them to promote their products without complying with the law. On the other hand, allowing doctors to prescribe off-label drug uses generates evidence, albeit weak, about uses that manufacturers refuse to study yet don’t refuse to profit from.

Judge Louis Brandeis realized the benefit in allowing states the liberty to be “little laboratories” in applying policy that does not necessarily correspond with the government viewpoint, and so does FDA.¹²⁶ Where manufacturers refuse to ensure the safety and efficacy of the drugs they promote, FDA allows individual doctors to engage in what essentially amounts to individual research thereby advancing the public interest and FDA’s mandate to advance the public health by encouraging innovation. If FDA were to ban off-label use, no innovation concerning off-label uses would occur at all because manufacturers aren’t studying them and doctors would not be able to experiment with them.

The authors also claim that FDA’s categorical ban subsumes manufacturer promotion of uses that are not only accepted but universally recognized as extremely valuable to the preservation of public health.¹²⁷ But this argument works both ways. FDA’s categorical ban not only subsumes the beneficial treatments but it also subsumes the harmful treatments. Without the

¹²⁵ Federal Food, Drug, and Cosmetic Act § 505(a) [21 U.S.C § 355(a)].

¹²⁶ *New State Ice Co. v Liebmann*, 52 S.Ct. 371.

¹²⁷ Coleen Klasmeier, Martin H. Redish, Off-Label Prescription Advertising, The FDA and the First Amendment: A Study in the Values of Commercial Speech Protection; *American Journal of Law and Medicine* 2011.

ability to separate the wheat from the chaff, FDA has no choice but to sweep up the good with the bad. Furthermore, uses that are accepted and universally recognized as beneficial would naturally have generated a plethora of evidence in the literature to support its approval and shouldn't need to be promoted. In other words, if so valuable and well known, these off-label uses should sell themselves. If manufacturers feel the need to promote these uses, they should collect the data, submit it to the FDA and make the off-label use on-label. This is the win-win solution that is in the best interest of the public and industry: objective, reliable, science-based evidence on the label with full transparency so the risks and benefits can be accurately weighed, individually at point of use.

The authors argue that FDA control of off-label use information is paternalistic and shows a lack of respect for the “citizenry’s ability to make lawful choices on the basis of truthful advocacy.”¹²⁸ The authors fail to recognize that patients as well as their doctors are a vulnerable population. It’s incomprehensible to think desperately ill laypersons can rationally analyze the veracity of a manufacturer’s claim and that doctors, in their choice to prescribe an off-label use, do so based on the information given to them via a sales representative. Any off-label use is an experiment, conducted by a doctor based on a hypothesis generated by potentially accurate but often incomplete and unreliable off-label promotion information, *and his own and other doctors experience*, in what essentially amounts to a series of uncontrolled studies with an n-value of one. So, it’s a vulnerable population with high stakes that warrants additional protection.

Finally, the authors claim that the FDA does not ban off-label *prescribing* of drugs simply because it is too inconvenient for them and “suppression of fully protected, potentially

¹²⁸ Id.

valuable expression is far too high a price to pay for government convenience”.¹²⁹ First, it’s highly debatable that this speech is, or even should be, *fully* protected, and second, the price that is too high to pay is for *the patients* who are deprived of objective, scientific based reliable information from which to make critical decisions affecting whether they will live or not, how long they will live, and what the quality of that experience will be. This, in contrast to pharmaceutical manufacturers who are deprived the ability to take advantage of ill patients’ desperate needs for cures with what amounts to the modern day version of quackery - the marketing and sale of a product without acceptable evidence for the efficacy and safety of whatever treatments, cures, regimens, or procedures are advocated, cloaked in a douse of fairy Godlobby dust. Congress recognized this fifty years ago when they passed the FDAC Amendments of 1962 based in part on reports that doctors could not adequately evaluate frequently misleading claims by drug manufacturers without a body of objective, reliable information.¹³⁰

The authors conclude that the FDA is using a hatchet to prevent all off-label promotion when they should be using a scalpel to dissect and separate truthful from untruthful claims thereby allowing them to prohibit *only* the untruthful claims.¹³¹ Well this is a job for Goliath. Separating the wheat from the chaff in this context requires the tool of scientific evidence. Who should pay for these tools - the U.S. taxpayers or the companies that stand to benefit from the sales of the truthful claims which FDA has dissected from the untruthful claims with the tools paid for by taxpayers? In any commercial world the burden is on the manufacturer to ensure their

¹²⁹ *Id.*

¹³⁰“Speeches by FDA Officials”: Linda A. Suydam, D.P.A.,FDLI Conference Keynote Address,Sept.13, 1999. <http://www.fda.gov/NewsEvents/Speeches/SpeechArchives/ucm054540.htm>.

¹³¹ Coleen Klasmeier, Martin H. Redish, Off-Label Prescription Advertising, The FDA and the First Amendment: A Study in the Values of Commercial Speech Protection; American Journal of Law and Medicine 2011.

products are safe and effective for any conceivable use of their product. Looking through the lens from FDA's viewpoint, a ban on manufacturer's off-label promotion is not bizarre at all, as the authors suggest. It's unfortunate that the judiciary has fallen prey to this rhetoric and overstepped their bounds in this highly specialized area which requires deference and flexibility to support a vital public health interest. Yes, we need someone to separate the wheat from the chaff but the U.S. taxpayers should not have to foot this bill to the enormous financial benefit of the pharmaceutical industry.

VI. Solutions

The court in *Caronia* got it wrong. In the context of drug safety and efficacy, the public health must outweigh the free speech rights of drug manufacturers. The fix to the tension between drug manufacturer's first amendment rights and the public's right to freedom from harm lies somewhere in between full protection and complete ban.

A. Disclaimers

Disclaimers are generally accepted as less restrictive ways to limit speech but fail here because the information which is not provided when a disclaimer is used is critical to meeting the statutory goals of the FDCA.

Disclaimers have long been used in the food and drug realm to save otherwise false and misleading claims. Precedents exist across the board from prescription to over-the-counter drugs to medical devices, to nutritionals and cosmetics. The benefit of using disclaimers is that they are less restrictive than a complete ban on speech, but in this context they would be inadequate. A disclaimer stating "this drug use has not been evaluated by FDA" does not enable the doctor or patient to adequately weigh the benefits and risks.

An example where use of a disclaimer makes sense is for Neosporin Scar Solution. Neosporin Scar Solution is an over-the-counter medical device indicated for the treatment of hypertrophic and keloid scars.¹³² The FDA mandated disclaimers, “this product is not sterile and does not contain antibiotics”, and “do not use on open wounds or unhealed skin”, effectively mitigate the potential that consumers may be misled and harmed by the name of the product.¹³³ The brand name Neosporin has long been associated with products containing the antibiotics neomycin, bacitracin, and polymyxin B. As such, consumers may readily believe that Neosporin Scar Solution has antibiotic properties and may be used on open wounds. Thus, the disclaimers noted above impart critical information to consumers that help them self-diagnose, self-select, and self-treat successfully. A disclaimer on this product which simply states, “this product has not been reviewed and approved by the FDA” would fail as an effective disclaimer because it does not impart the critical information need to use the product safely and effectively.

B. Clinical Evidence

Promoting on-label drug uses based on clinical evidence pursuant to an effective NDA is not restricted. Manufacturers can avail themselves to various types of clinical evidence to get their off-label claims approved and made on-label.¹³⁴ Instead of two adequate and well-controlled clinical studies, they can refer to peer reviewed journal articles to gain approval for their drugs’ off-label use.¹³⁵ Although the studies described in peer review articles are typically not scientifically robust, and studies with negative results aren’t typically submitted for peer

¹³² FDA 510(k) Premarket Notification Searchable Database: Neosporin Scar Solution K024160 <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=10364>.

¹³³ Id.

¹³⁴ FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biologic, May 1998.

¹³⁵ Id.

review and publication, the FDA does accept peer review articles in support of approvals for additional indications of an already approved drug.¹³⁶ FDA has historically encouraged firms to submit scientific evidence about new uses in supplemental applications with the aim of getting the approved data in the labeling where they can do most good.¹³⁷

The conduct of clinical studies and the process of scientific fact-finding is the backbone of public health protection.¹³⁸ The need for adequate and well-controlled clinical studies of new drugs is evident from the long history of public health setbacks in the United States. It is completely unacceptable that patients should be assuming the risk of using a drug on the basis of deceptive promotion.¹³⁹ Sound evidence of effectiveness is crucial to the FDA benefit versus risk assessment of a particular drug but what comprises evidence of effectiveness has been the subject of much debate. Pursuant to the Food Drug and Modernization Act (FDAMA) of 1997, Congress directed the FDA to provide guidance on the “circumstances in which published matter may be the basis for approval of a supplemental application for a new indication, and on data requirements that will avoid duplication of previously submitted data by recognizing the availability of data previously submitted in support of an original application to support approval of a supplement application.”¹⁴⁰ In short, it describes the scientific rigor needed when less than two adequate and well-controlled studies are conducted or available.

The FDA “*Guidance for Industry –Providing Clinical Evidence of Effectiveness for Human Drugs and Biologics*”, describes the qualitative and quantitative standards for supporting

¹³⁶ Id.

¹³⁷ “Speeches by FDA Officials” Linda A. Suydam, D.P.A., FDLI Conference Keynote Address, Sept.13, 1999 <http://www.fda.gov/NewsEvents/Speeches/SpeechArchives/ucm054540.htm>.

¹³⁸ Id.

¹³⁹ Id.

¹⁴⁰ FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biologic, May 1998.

safety and effectiveness and encourages the submission of Supplemental New Drug Applications (SNDAs) to add new uses to the labeling of approved drugs.¹⁴¹ It provides the scientific justification for the legal standard of substantial evidence.¹⁴² As legally defined in the FDCA, substantial evidence is “evidence consisting of adequate and well controlled investigations including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug product 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 or proposed labeling thereof.”¹⁴³ In this Guidance, FDA has interpreted this statutory requirement and described various ways to establish it.¹⁴⁴ Pursuant to this Guidance, manufacturers have a number of options for pursuing approval of an off-label use with less than usual the quantity or quality of data required.¹⁴⁵

In addition, while full reports showing safety and efficacy by the sponsor are generally needed, the FD&C Act itself allows drugs to be approved based on less evidence.¹⁴⁶ Although not as scientifically robust, referencing someone else’s data and published literature reports can support approval pursuant to a 505(b)(2) application.¹⁴⁷ The 505(b)(2) Application results in a comprehensive summary of the data relevant to the use in the product’s labeling and gives doctors and their patients unbiased and objective information to weigh benefits versus risks at point of use via the package insert which accompanies each package of the drug. FDA accepts

¹⁴¹ *Id.*

¹⁴² *Id.*

¹⁴³ Federal Food, Drug, and Cosmetic Act 505 § (21 U.S.C § 355).

¹⁴⁴ FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biologic, May 1998

¹⁴⁵ *Id.*

¹⁴⁶ 505(b) Federal Food, Drug and Cosmetic Act.

¹⁴⁷ 505(b)(2) Federal Food, Drug and Cosmetic Act.

this type of data and approves 505(b)(2) applications on a regular basis.¹⁴⁸ In fact, 505(b)(2) applications typically comprise almost half of all applications approved each year.¹⁴⁹

VII. Conclusion

Off-label drug promotion must continue to be restricted. Statutory interpretation concludes that Congress intended for FDA to take whatever steps necessary to protect the public from unsafe and ineffective drugs. Off-label promotion is now constitutionally protected speech but its restriction survives heightened scrutiny and is thus justified. Public policy mandates that public health trump freedom of speech in the context of off-label drug advertising and promotion of drugs. Supplemental NDAs and the 505(b)(2) mechanism already provide ways for manufacturers to gain approval for other uses of a drug based on less than full investigations of safety and efficacy. Pharmaceutical manufacturers need to recognize and embrace the benefits of adequate, science-based, reliable information to meet their responsibility in ensuring that the public gets the information they need to achieve successful outcomes when using the drugs they promote. The appropriate way to disseminate information about off-label uses is through independent symposia, educational sessions, and professional meetings while manufacturers *contemporaneously* investigate the uses in scientifically driven adequate and well controlled studies. In this way, patients will still have access to potentially valuable off-label uses but harmful uses will be brought to light sooner thereby limiting their exposure to the public.

¹⁴⁸ Id.

¹⁴⁹ CDER Drug and Biologic Approvals Reports, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/default.htm>.