

COMMENTS

What Is “False or Misleading” Off-Label Promotion?

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INTRODUCTION

In the late 1990s, the drugmaker GlaxoSmithKline obtained some exciting research results about the antidepressant Wellbutrin.¹ Rather than interfering with sex drive and sleep cycle like many competing products, Wellbutrin appeared to have positive side effects, like suppressing appetite and reducing cigarette cravings.² GlaxoSmithKline could have sought formal endorsement of these findings from the FDA. Instead, the drugmaker embarked on a marketing campaign that would lead to one of the largest health care settlements in history.³

A federal complaint describes how GlaxoSmithKline executives designed and systematically executed “Operation Hustle” to perform follow-up studies and generate buzz about the use of Wellbutrin for conditions that frequently accompany depression, including weight gain, sexual dysfunction, and attention deficit hyperactivity disorder.⁴ The firm sponsored group seminars to

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¹ See United States’ Complaint, *United States v GlaxoSmithKline PLC*, Civil Action No 11-10398-RWZ, *21, 37–38 (D Mass filed Oct 26, 2011) (“GSK Complaint”), archived at <http://perma.cc/QD57-J849> (describing various findings that GlaxoSmithKline compiled regarding Wellbutrin’s effectiveness for off-label uses and its mechanism of action).

² See id at *35–38.

³ See Press Release, *GlaxoSmithKline to Plead Guilty and Pay \$3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data* (US Department of Justice, July 2, 2012), archived at <http://perma.cc/A6HM-K5RF> (“GSK Press Release”); Settlement Agreement, *United States v GlaxoSmithKline PLC* *7 (July 2, 2012) (“GSK Settlement”), archived at <http://perma.cc/6PKM-EGGZ>.

⁴ GSK Complaint at *25 (cited in note 1). Though specific details of the data are unavailable, GlaxoSmithKline’s studies were likely narrower in scope than standard clinical trials, targeting particular patient populations. For example, one study is described as testing twenty-five patients for eight weeks. See id at *21. This design is

provide physicians with details about the scientific support for its claims and dispatched sales representatives to doctors' offices to tout Wellbutrin as a "happy, horny, skinny pill."⁵ Though GlaxoSmithKline's tests lacked FDA endorsement, the firm's marketing strategies worked.⁶ Sales increased by a third in less than a year.⁷

GlaxoSmithKline's successful campaign led to a slew of lawsuits accusing the company of promoting drugs for unapproved ("off-label") uses.⁸ None of the complaints, however, actually claimed that GlaxoSmithKline had made false or misleading statements about Wellbutrin. The complaints acknowledged that physicians who prescribed Wellbutrin understood the promotional nature of GlaxoSmithKline's messaging. One complaint even recounted how a physician described the company's seminar speaker as a "drug whore."⁹ In fact, despite all the negative publicity, Wellbutrin remains a hugely popular drug, with some prominent physicians endorsing the scientific support for its beneficial side effects.¹⁰

The Wellbutrin story raises difficult questions about how to distinguish harmful off-label marketing from information that physicians find useful when making prescribing decisions. In particular, how should courts determine whether a physician's reliance on off-label claims is the result of useful education as opposed to successful duping? Since the Wellbutrin case settled, developments in the federal courts have brought this question to prominence. This Comment provides an answer. Part I describes the current legal framework for regulating drug advertising and explains the emerging importance of developing a test for identifying "false or misleading" off-label promotion. Part II explains the framework for identifying false or misleading advertisements

typical for a merely exploratory study—while large enough to provide statistically significant results about weight loss over the first few weeks of Wellbutrin use, this study's design does not meet the expansive FDA requirements of double blinding, placebo control, and randomization. See 32 CFR § 314.126(b)(2)(i).

⁵ GSK Complaint at *19, 34–39 (cited in note 1).

⁶ See id at *21–23.

⁷ See id at *25.

⁸ See id at *2–3 (listing various civil actions that had been separately filed against GlaxoSmithKline and that were later consolidated into a single action upon government intervention).

⁹ GSK Complaint at *32 (cited in note 1).

¹⁰ See Sari Botton, *The Happy, Sexy, Skinny, Pill?* (Harper's Bazaar, Feb 19, 2014), archived at <http://perma.cc/J8QS-RULX>.

under the Lanham Act¹¹ and the Federal Trade Commission Act¹² (“FTC Act”) and demonstrates that this framework is appropriate for the off-label-promotion context. Part III explores how the false advertising approach can be adapted to the off-label context.

I. THE LAW OF OFF-LABEL PROMOTION

Though off-label promotion is at the center of numerous active lawsuits and a national policy debate, courts have not yet addressed what constitutes “false or misleading” off-label speech. This Part provides the legal background pertinent to defining the term. Section A describes how the government ensures the safety and effectiveness of new drugs. Section B addresses the legal status of off-label promotion. Section C explains why that legal status has, until recently, obviated the need to devise a framework for identifying false or misleading off-label speech, and why recent cases will require courts to do so now.

A. The Food, Drug, and Cosmetic Act’s Drug Safety and Effectiveness Requirements

The Federal Food, Drug, and Cosmetic Act¹³ (FDCA) requires drugmakers to obtain FDA approval before marketing a new drug.¹⁴ The approval process begins when a drug company identifies a promising product.¹⁵ The drug company files a New Drug Application (NDA) to alert the FDA of the company’s intention to seek approval for the drug and request that the FDA begin the new-drug evaluation process.¹⁶ The FDA estimates that this evaluation typically takes more than eight years to complete.¹⁷

The FDA can approve a new drug only if extensive scientific studies demonstrate that the drug is safe and effective.¹⁸ These

¹¹ 15 USC § 1051 et seq.

¹² 15 USC § 41 et seq.

¹³ 21 USC § 301 et seq.

¹⁴ See 21 USC § 355(a).

¹⁵ See Peter Barton Hutt, Richard A. Merrill, and Lewis A. Grossman, *Food and Drug Law* 669–70 (Foundation 4th ed 2014).

¹⁶ See 21 USC § 355(a)–(b).

¹⁷ See *Drug Development and Review Definitions* (US Food and Drug Administration, Mar 30, 2015), archived at <http://perma.cc/L57E-SBH2>.

¹⁸ See 21 USC § 355(d).

studies, known as clinical trials, consist of highly structured experiments jointly designed by the FDA and the drugmaker.¹⁹ The data obtained from these trials must affirmatively demonstrate that the drug is safe and must yield “substantial evidence” that the drug will be effective for the use for which it is to be marketed.²⁰ If the drug meets these threshold requirements, the FDA uses the clinical trial data to determine whether the balance of the drug’s risks and benefits supports approval for the specified use.²¹

The FDA grants approval on a use-by-use basis. Since the FDCA defines a “new drug” as one that is “not generally recognized, among experts . . . as safe and effective” for a particular use, a “new drug” can be either an entirely new substance or a preexisting drug that the drugmaker seeks to have prescribed for a different illness or condition.²² In either case, the drugmaker must conduct clinical trials if it wishes to obtain FDA approval for the use.²³ Once the FDA grants approval for a use, the drugmaker may list the use on the drug’s label and market the drug for that use.²⁴

B. The Statutory and Regulatory Framework for Policing Off-Label Promotion

There is considerable debate about whether pharmaceutical companies should be allowed to promote drugs for off-label uses. When litigating cases under the FDCA, the FDA has taken the position that off-label promotion is harmful because it undermines drugmakers’ incentives to seek approval for new uses of their products.²⁵ The FDA’s view reflects the concern that drug

If the Secretary finds . . . [that the application does not] include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed . . . [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 . . . [the Secretary] shall issue an order refusing to approve the application.

¹⁹ See 21 USC § 355(b)(5)(B), (d).

²⁰ 21 USC § 355(d).

²¹ See Hutt, Merrill, and Grossman, *Food and Drug Law* at 729 (cited in note 15).

²² 21 USC § 321(p)(1).

²³ See 21 USC § 355(b)(5)(B).

²⁴ See 21 CFR § 201.100(c)(2).

²⁵ See, for example, *Thompson v Western States Medical Center*, 535 US 357, 368–69 (2002) (describing the FDA’s argument that “individual doctors . . . cannot be relied upon” to make “scientifically valid” judgments about safety and effectiveness); *Washington Legal Foundation v Friedman*, 13 F Supp 2d 51, 56–57 (DDC 1998); Coleen Klasmeier and

manufacturers engaging in off-label promotion are seeking to evade the regulatory process, either because they wish to avoid the costs of conducting clinical trials, or because their data would not pass muster with the FDA.²⁶ If that were so, the argument goes, doctors who received information about off-label uses might be encouraged to prescribe treatments that would not meet the FDA’s high approval standards.²⁷

No federal statute or regulation prohibits off-label promotion, however. Because of this, the government can prosecute drug companies for off-label promotion only indirectly, under the FDCA’s prohibition of misbranding.²⁸ The term “misbranding” refers to a variety of behaviors,²⁹ and companies that engage in misbranding may be subject to civil and criminal penalties.³⁰

Two forms of misbranding under the FDCA are relevant to off-label promotion: misbranding based on false or misleading advertising³¹ and misbranding based on drug-labeling requirements.³² Statutory provisions prohibiting each of these types of

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, 335 n 98 (2011) (noting that the FDA has asserted “in the off-label promotion context that adequate protection of the public health requires unwavering enforcement of the high standards for efficacy data”). Importantly, the FDA’s position is not entitled to deference. The Supreme Court does not defer to agency positions advanced in litigation that are “wholly unsupported by regulations, rulings, or administrative practice.” *Bowen v Georgetown University Hospital*, 488 US 204, 212 (1988). The FDA has not promulgated regulations that specifically ban off-label promotion, and any such regulations would likely violate the First Amendment. See Part I.C.1.

²⁶ See Hutt, Merrill, and Grossman, *Food and Drug Law* at 925 (cited in note 15). This concern is particularly acute in light of the FDA’s lengthy premarket-approval process. See *Drug Development and Review Definitions* (cited in note 17).

²⁷ See Kate Greenwood, *The Ban on “Off-Label” Pharmaceutical Promotion: Constitutionally Permissible Prophylaxis against False or Misleading Commercial Speech?*, 37 *Am J L & Med* 278, 294 (2011) (“Busy, boundedly rational physicians are an inadequate check on companies’ tendencies to overstate the scientific support for off-label uses.”); Klasmeier and Redish, 37 *Am J L & Med* at 335 n 98 (cited in note 25).

²⁸ See 21 USC § 331(a)–(c) (prohibiting the misbranding of drugs, as well as the transportation and receipt of misbranded drugs in interstate commerce). See also Marc J. Scheineson and 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, 204–07 (2013) (describing the statutory framework under which the FDA regulates off-label promotion).

²⁹ For a complete list of such behaviors, see 21 USC § 352 (defining a drug as “misbranded” if, for example, the drug’s packaging fails to prominently display certain statutorily specified information, the drug’s label recommends a health-endangering dosage, or the drug is offered for sale under another drug’s name).

³⁰ See 21 USC § 333.

³¹ See 21 USC § 352(bb).

³² See 21 USC § 352(f).

misbranding allow the FDA to penalize companies for certain communications to physicians and consumers. The advertising provision prohibits false or misleading promotional statements,³³ while the labeling provision prohibits marketing drugs without providing sufficient guidance for their use.³⁴ This Section first describes both forms of misbranding. It then turns to the effect of the government's decision to focus on prosecuting off-label promotion through the labeling provision rather than the advertising provision.

1. Misbranding based on false or misleading advertising.

The form of misbranding most clearly pertinent to off-label promotion relates to drug advertising. Under the FDCA, a drug company may be liable for misbranding if the drug's "advertising or promotion . . . is false or misleading."³⁵ According to the regulations that interpret this provision, an advertisement is false or misleading if it is not an accurate representation of the drug's safety and effectiveness.³⁶

The regulations associated with the advertising-related misbranding provision provide appropriate guidelines for sorting useful off-label promotion from that which might lead doctors to prescribe unsafe or ineffective drugs. Rather than outlining broadly applicable benchmarks for determining whether a promotional statement meets a satisfactory standard of scientific certainty, the regulations urge a fact-specific analysis. Specifically, an advertising claim is false or misleading if it does not reflect the weight of "substantial evidence or substantial clinical experience" with the drug.³⁷ The regulations provide an extensive list of behaviors that might constitute misrepresentation, ranging from improper data analysis³⁸ to the overstatement of research results.³⁹ Notably, the regulations are agnostic about FDA approval status and theoretically apply to both on- and off-label marketing claims.

³³ 21 USC § 352(bb).

³⁴ 21 USC § 352(f).

³⁵ 21 USC § 352(bb).

³⁶ 21 CFR § 202.1(e)(6).

³⁷ 21 CFR § 202.1(e)(6)(i).

³⁸ 21 CFR § 202.1(e)(7)(ii)–(v).

³⁹ 21 CFR § 202.1(e)(7)(i).

2. Misbranding based on drug-labeling requirements.

Though the advertising provision is a precise and apposite tool for deterring harmful off-label promotion, the government has generally taken the more circuitous approach of demonstrating misbranding through a failure to meet the FDCA’s labeling requirements. These labeling requirements provide that a drug is misbranded if its label does not contain “adequate directions for us[ing]” the drug.⁴⁰ The instructions on the label must be sufficient to allow practitioners to “use the drug safely and for the purposes for which it is intended.”⁴¹ To prove misbranding, the government must show both that the drugmaker intended for doctors to prescribe the drug for a particular use, and that the label does not provide adequate directions for that use.

This interpretation of the labeling provision requires a perfect correspondence between the drugmaker’s intended uses and the uses listed on the label. Since a drug’s label may include instructions only for FDA-approved uses,⁴² it is impossible for the label to provide “adequate” directions for engaging in off-label use. Thus, under the FDA’s interpretation of the labeling provision, a drug is misbranded whenever a drug company intends that a drug be prescribed for an off-label use.⁴³

This interpretation is damning for off-label promotion because, according to FDA regulations, a drugmaker’s promotional statements are evidence of its intended use for the drug.⁴⁴ A drugmaker’s “advertising matter, or oral or written statements” may be evidence of objective intent.⁴⁵ FDA regulations go so far as to conclude that a drugmaker’s knowledge “that [its drug] is . . . offered and used for a purpose for which it is neither labeled nor advertised” may demonstrate that the drugmaker intended

⁴⁰ 21 USC § 352(f). For a concise explanation of labeling requirements, see Luke Dawson, Note, *A Spoonful of Free Speech Helps the Medicine Go Down: Off-Label Speech & the First Amendment*, 99 Iowa L Rev 803, 810–11 (2014).

⁴¹ 21 CFR § 201.100(c)(1).

⁴² See 21 USC § 355(d) (stating that NDAs must be rejected if there is insufficient evidence to support the drug’s proposed labeling).

⁴³ See, for example, *United States v Caronia*, 703 F3d 149, 154–55 (2d Cir 2012) (explaining that “[the FDA] has construed the FDCA to prohibit promotional speech as misbranding itself” by treating off-label promotional speech as dispositive evidence that the drugmaker intends the drug to be used for an unapproved purpose).

⁴⁴ See 21 CFR § 201.128 (providing that such intent may be “determined by [a drugmaker’s] expressions or may be shown by the circumstances surrounding the distribution of the [drug]”).

⁴⁵ 21 CFR § 201.128.

for the drug to be prescribed for that use—even if a third party made the statements.⁴⁶

Since virtually any discussion of off-label use can be evidence that a drug does not contain “adequate directions for” each intended use of that drug, the FDA’s construction of the FDCA’s labeling requirements effectively makes off-label promotion per se unlawful.⁴⁷ Under this interpretation, the government can prove misbranding simply by demonstrating that the company engaged in off-label promotion. Because proving that a promotional statement is directed toward an off-label use is more straightforward than proving that an off-label statement is false or misleading, the government’s interpretation of the labeling provision has obviated the need to pursue claims under the advertising provision.

The government’s chosen theory of liability is unsurprising. In the FDA’s view, off-label promotion not only poses a potential threat to patient safety but also undermines the substantial government interest in ensuring that patients benefit from the effectiveness evaluation included in the NDA process.⁴⁸ Though courts sometimes acknowledge the curious “asymmetry” inherent in a legal regime that allows off-label prescriptions but not off-label promotion,⁴⁹ many have accepted the FDA’s construction of the statute.⁵⁰ The government has prosecuted numerous

⁴⁶ 21 CFR § 201.128.

⁴⁷ John E. Osborn, *Can I Tell You the Truth? A Comparative Perspective on Regulating Off-Label Scientific and Medical Information*, 10 Yale J Health Pol, L & Ethics 299, 309 (2010), quoting 21 USC § 352(f)(1). See also Osborn, 10 Yale J Health Pol, L & Ethics at 308–09 (citations omitted) (“[T]he Act’s prohibition of false or misleading labeling is transformed by the agency into an effective prohibition on any advertisement, promotional message, or discussion that is not ‘consistent with’ the approved product labeling, or otherwise concerns any use that has not been approved expressly by the FDA.”).

⁴⁸ See *Western States Medical Center*, 535 US at 369:

[T]he safety and effectiveness of a new drug needs to be established by rigorous, scientifically valid clinical studies because impressions of individual doctors, who cannot themselves compile sufficient safety data, cannot be relied upon. . . . [T]he Government has every reason to want as many drugs as possible to be subject to [the] approval process.

But see *Caronia*, 703 F3d at 153 (“Indeed, courts and the FDA have recognized the propriety and potential public value of unapproved or off-label drug use.”).

⁴⁹ See, for example, *In re Schering Plough Corp Intron/Temodar Consumer Class Action*, 678 F3d 235, 240 (3d Cir 2012).

⁵⁰ See, for example, *United States v Caputo*, 288 F Supp 2d 912, 920 (ND Ill 2003) (“[P]romoting off-label uses makes [a product] misbranded.”).

pharmaceutical companies for off-label promotion through its construction of the FDCA’s labeling provision.⁵¹

3. The FDA’s de facto authority to control off-label speech.

With off-label speech effectively banned, the FDA ultimately has the power to delineate the boundaries of acceptable off-label promotion. Historically, the agency has set these boundaries through the use of both its rulemaking authority and its prosecutorial discretion. The agency has recognized that, in some cases, off-label promotion can further medical science.⁵² To capture these benefits, the FDA formally condones off-label communication in two limited situations: when the communication meets the requirements of the scientific-exchange exception to the general bar on off-label speech, and when the communication is transmitted in conjunction with a drug company’s participation in the Investigational New Drug (IND) application program.

First, the FDA’s scientific-exchange exception consists of regulations that permit drugmakers and physicians to communicate the underlying science about off-label uses.⁵³ Knowledge about new uses for a drug might emerge after the drug’s initial approval—particularly in heavily researched fields of medicine that are constantly evolving.⁵⁴ Since doctors are free to prescribe drugs for both FDA-approved and unapproved uses,⁵⁵ communication with drugmakers can allow doctors to obtain and use new research findings without waiting for the FDA to complete its lengthy approval process.⁵⁶ Such off-label prescriptions can have tangible public health benefits—the medical community considers some off-label uses to be “state of the art” procedures for treating certain conditions.⁵⁷

To facilitate such developments, the scientific-exchange exception allows drug companies to publish information about

⁵¹ See, for example, *Caronia*, 703 F3d at 154.

⁵² See, for example, *Washington Legal Foundation*, 13 F Supp 2d at 56 (“Even the FDA acknowledges that in some specific and narrow areas of medical practice, practitioners consider off-label use to constitute the standard of good medical care.”).

⁵³ See Hutt, Merrill, and Grossman, *Food and Drug Law* at 925–26 (cited in note 15).

⁵⁴ See J. Howard Beales III, *Economic Analysis and the Regulation of Pharmaceutical Advertising*, 24 Seton Hall L Rev 1370, 1386 (1994).

⁵⁵ See *Buckman Co v Plaintiffs’ Legal Committee*, 531 US 341, 351 n 5 (2001).

⁵⁶ See Beales, 24 Seton Hall L Rev at 1387 (cited in note 54).

⁵⁷ James M. Beck and Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 Food & Drug L J 71, 85 (1998).

off-label uses in medical journals and then distribute unabridged, unaltered copies of those published articles to physicians.⁵⁸ At a minimum, the articles must be subjected to peer review by independent experts who disclose any conflicts of interest, and each article must be published in a journal that is not funded by the drugmaker.⁵⁹

Alternatively, a drug company that wishes to communicate information more informally may do so by first submitting an IND application to officially begin the exploration of a new use for a previously approved drug.⁶⁰ Then, throughout the investigation, the drug company may share “information concerning the drug, including dissemination of scientific findings in scientific or lay media.”⁶¹ Though the drug company cannot represent that the drug is “safe or effective” for the use under investigation,⁶² the ability to disseminate scientific information without meeting the strict standards of the scientific-exchange exception allows drug companies to convey preliminary research results in more informal ways.

Even with regard to communications disseminated under these authorized exceptions to the off-label-promotion ban, the FDA reserves the right to independently determine whether off-label speech is false or misleading.⁶³ FDA guidance provides several examples of what constitutes false or misleading communication.⁶⁴ Based on these examples, it is clear that the FDA holds drugmakers to a higher standard than mere truthfulness. For instance, a claim in a scientific or medical journal is misleading if it is based on a clinical study that would not meet the specific requirements of the FDA clinical trial process—even if the

⁵⁸ See *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* (US Food and Drug Administration, Jan 2009) (“FDA Guidance on Scientific Exchange”), archived at <http://perma.cc/2X97-KEBJ>.

⁵⁹ See *id.*

⁶⁰ See 21 CFR § 312.20(a).

⁶¹ 21 CFR § 312.7(a).

⁶² 21 CFR § 312.7(a).

⁶³ See FDA Guidance on Scientific Exchange (cited in note 58).

⁶⁴ See *id.* (deeming information in a scientific or medical journal to be “false or misleading” if, for example, it discusses a clinical investigation that the FDA has previously deemed inadequate or if it mischaracterizes the extent to which its claims conflict with “well-controlled clinical investigations”).

research results were overwhelmingly persuasive or accompanied by a disclaimer.⁶⁵

However, since the FDA does not regularly approve or disapprove scientific information before a drug company communicates it,⁶⁶ the exact standard for what constitutes acceptable off-label communication is unclear.⁶⁷ Drug companies that wish to minimize their chance of facing an FDA enforcement action thus have an incentive to withhold information about uses that are not yet supported by studies conducted in accordance with FDA best practices.

This uncertainty is problematic because it impedes the very off-label communications that are most valuable to the development of medical science.⁶⁸ Off-label research is particularly useful when it pertains to uses for which a drugmaker is unlikely to seek FDA approval. For example, off-label promotion may be the best means of disseminating information about a new use that is discovered late in the life of a product's patent, when a drugmaker can no longer justify the cost of seeking approval for new uses.⁶⁹

Most commonly, off-label information pertains to discoveries about which it is too risky or expensive to seek FDA approval, such as weak health effects or effects that occur in a small subset of the potential patient population.⁷⁰ Though the exact benefits of such information may be speculative, patients stand to gain in the long run from information dissemination, particularly when the alternative treatment options are fungible. For example, data suggesting that Wellbutrin improves impulse control might help to inform a physician's marginal decision about

⁶⁵ See *id.*

⁶⁶ See *id.*

⁶⁷ Reference to prior FDA warning letters would likely provide insufficient guidance for drug companies, because most warning letters are fairly vague and the details of a drug company's resolution of the warning letter are not published. Moreover, it is not clear that one drug company could glean much regarding how to communicate about its own experiment from analyzing communications about other companies' studies, because experimental designs and approaches vary widely. See Scheineson and Cuevas, 68 *Food & Drug L J* at 214 (cited in note 28) (noting the breadth of the FDA's various interpretations of “misleading speech” in the context of off-label promotion).

⁶⁸ See Randall S. Stafford, *Regulating Off-Label Drug Use—Rethinking the Role of the FDA*, 358 *New Eng J Med* 1427, 1427 (2008).

⁶⁹ See Beales, 24 *Seton Hall L Rev* at 1387 (cited in note 54).

⁷⁰ See Aaron S. Kesselheim, *Off-Label Drug Use and Promotion: Balancing Public Health Goals and Commercial Speech*, 37 *Am J L & Med* 225, 253–54 (2011) (explaining how off-label information might uniquely benefit small subsets of patients).

which antidepressant to prescribe for a gambling addict.⁷¹ In such cases, the off-label use of a drug may be a patient's best treatment option.⁷² Because the scientific-exchange and IND exceptions do not provide for such communication, neither approach precisely distinguishes between helpful and harmful off-label speech.

C. Emerging Questions about the Definition of False or Misleading Off-Label Speech

As a result of the government's effective ban on off-label promotion and the high standard for the scientific-exchange exception,⁷³ courts have rarely had to grapple with the complex issue of distinguishing between misleading and nonmisleading speech about off-label uses.⁷⁴ This is likely to change for two reasons. First, federal courts are increasingly recognizing corporate free speech rights, which may render the FDA's construction of the FDCA unconstitutional. Second, recent cases have created incentives for private parties to pursue legal action for false or misleading speech under other statutes.

1. Off-label promotion and the First Amendment.

Drugmakers have argued that an outright ban on off-label speech—including speech that is neither false nor misleading—violates the First Amendment.⁷⁵ Because off-label *prescriptions* are “lawful, the argument goes, it must also be lawful to tell [doctors] about them.”⁷⁶ Though the Supreme Court has recognized that maintaining the integrity of the NDA process is a substantial government interest that might support speech regulation,⁷⁷ such regulation must not be “more extensive than [] necessary” to achieve that objective.⁷⁸ When determining whether the regulation of commercial speech is more extensive than

⁷¹ See generally *Choosing Antidepressants for Adults: Clinician's Guide* (Agency for Healthcare Research and Quality, Aug 2007), archived at <http://perma.cc/WLA4-48VZ>.

⁷² See Kesselheim, 37 Am J L & Med at 238 (cited in note 70).

⁷³ See Part I.B.3.

⁷⁴ See Scheineson and Cuevas, 68 Food & Drug L J at 212 (cited in note 28) (noting the lack of precedent addressing the question of how “misleading” should be defined in the context of off-label speech).

⁷⁵ See, for example, *Caronia*, 703 F3d at 152.

⁷⁶ *United States v Caputo*, 517 F3d 935, 938 (7th Cir 2008).

⁷⁷ See *Western States Medical Center*, 535 US at 369.

⁷⁸ Id at 371, quoting *Central Hudson Gas & Electric Corp v Public Service Commission of New York*, 447 US 557, 566 (1980).

necessary, courts consider factors such as whether the commercial speaker has alternative channels for communicating truthful, nonmisleading information, and whether the government could adopt a less-speech-restrictive regulatory approach.⁷⁹

The drugmakers’ free speech argument has recently gained traction. In *Thompson v Western States Medical Center*,⁸⁰ for example, the Supreme Court held that FDA restrictions on advertising for compounded drugs were unconstitutional.⁸¹ Compounded drugs—which are medications that combine two or more FDA-approved drugs to form a single medication—are not subject to FDA regulation.⁸² The Court determined that it would be nonsensical to allow drug companies to make, and doctors to prescribe, compounded drugs but not allow drug companies to promote them.⁸³ The Court determined that the government can have no interest in “preventing the dissemination of truthful commercial information in order to prevent members of the public from making bad decisions with the information.”⁸⁴

In the same vein, the Court specifically held in *Sorrell v IMS Health Inc*⁸⁵ that “[s]peech in aid of pharmaceutical marketing [] is a form of expression protected by the Free Speech Clause of the First Amendment.”⁸⁶ The Court noted that the “fear that people would make bad decisions if given truthful information” cannot, alone, justify content-based regulations of pharmaceutical marketing,⁸⁷ particularly when the audience consists of “sophisticated and experienced” consumers such as prescribing physicians.⁸⁸ Thus, the Court ruled that restrictions on pharmaceutical-marketing speech are subject to heightened

⁷⁹ See *44 Liquormart, Inc v Rhode Island*, 517 US 484, 529–30 (1996) (O’Connor concurring). See also *Sorrell v IMS Health Inc*, 131 S Ct 2653, 2667–68 (2011) (placing the burden on the government to demonstrate that a statute restricting commercial speech “directly advances a substantial governmental interest and . . . is drawn to achieve that interest”).

⁸⁰ 535 US 357 (2002).

⁸¹ *Id* at 373–77.

⁸² See *id* at 361, 364.

⁸³ See *id* at 372–77.

⁸⁴ *Western States Medical Center*, 535 US at 374. See also *id* at 375, citing *Virginia State Board of Pharmacy v Virginia Citizens Consumer Council, Inc*, 425 US 748, 769–70 (1976).

⁸⁵ 131 S Ct 2653 (2011).

⁸⁶ *Id* at 2659.

⁸⁷ *Id* at 2670–71, quoting *Western States Medical Center*, 535 US at 374.

⁸⁸ *Sorrell*, 131 S Ct at 2671, quoting *Edenfield v Fane*, 507 US 761, 775 (1993).

scrutiny,⁸⁹ so long as the speech in question is not false or misleading.⁹⁰

Though *Western States Medical Center* and *Sorrell* addressed pharmaceutical-marketing issues other than off-label marketing, both opinions are written in broad language that implies that all restrictions on drug-marketing speech—including those meant to ensure patient safety—are now subject to strict scrutiny. Applying this Supreme Court precedent to off-label marketing, the Second Circuit concluded in *United States v Caronia*⁹¹ that off-label marketing cannot be per se unlawful.⁹² Because independent researchers can speak freely about off-label uses, an outright ban on off-label speech by pharmaceutical companies would constitute an impermissible, speaker-based restriction under *Sorrell*.⁹³ Noting that there are numerous less restrictive alternatives available to ensure that drug companies communicate responsibly,⁹⁴ the court held that “the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug.”⁹⁵ In other words, in the Second Circuit, off-label promotion that is not false or misleading is not per se unlawful.⁹⁶

The *Caronia* decision has brought into focus the question of what constitutes false or misleading promotional speech. Many commentators have argued that *Caronia* will be the first in a series of decisions leading to a safe harbor for truthful off-label promotional speech.⁹⁷ Indeed, several district courts have already cited *Caronia* for the proposition that the FDCA does not prohibit truthful, nonmisleading off-label promotion.⁹⁸

⁸⁹ *Sorrell*, 131 S Ct at 2663–67.

⁹⁰ *Id* at 2672, citing *Western States Medical Center*, 535 US at 373.

⁹¹ 703 F3d 149 (2d Cir 2012).

⁹² *Id* at 164 (holding that FDA prohibitions on off-label speech are subject to heightened scrutiny).

⁹³ *Id* at 165, 168.

⁹⁴ *See id* at 167.

⁹⁵ *Caronia*, 703 F3d at 169.

⁹⁶ *Id* at 164, 165 n 10.

⁹⁷ *See*, for example, John C. Richter and Daniel C. Sale, *The Future of Off-Label Promotion Enforcement in the Wake of Caronia—Toward a First Amendment Safe Harbor*, 14 *Sedona Conf J* 19, 34 (2013).

⁹⁸ *See*, for example, *Schouest v Medtronic, Inc.*, 13 F Supp 3d 692, 702–03 (SD Tex 2014); *Schuler v Medtronic, Inc.*, 2014 WL 988516, *1 (CD Cal); *In re Celexa and Lexapro Marketing and Sales Practices Litigation*, 2014 WL 3908126, *7 (D Mass); *Dawson v Medtronic, Inc.*, 2013 WL 4048850, *5 (D SC).

Whether the circuits agree that off-label marketing is not per se unlawful, the government will likely respond to the possibility of First Amendment protection by more consistently alleging that off-label promotions are false or misleading (under the FDCA’s advertising-based misbranding provision) when prosecuting drug companies and their representatives.⁹⁹ Indeed, the government has brought charges of false or misleading off-label promotion in several cases since *Caronia*.¹⁰⁰ The government’s decision to consistently allege that drug companies have engaged in false or misleading off-label promotion is a departure from the FDA’s past failure to distinguish its claims of misbranding due to false or misleading advertising from its claims of misbranding due to a failure to meet the FDA’s labeling requirements.¹⁰¹

2. Incentives for private-party claims.

The definition of false or misleading off-label promotion is also of great interest to nongovernmental plaintiffs. For example, health insurers pay much higher reimbursement costs when an off-label promotion leads physicians to prescribe new and expensive on-patent drugs rather than existing, cheaper treatments.¹⁰² Several recent rulings increase private parties’ incentives to take legal action to rectify such damages.

Most significant among these cases is the Supreme Court’s decision in *POM Wonderful LLC v Coca-Cola Co.*¹⁰³ There, the Court held that the government’s exclusive jurisdiction to prosecute claims of misleading advertising under the FDCA does not

⁹⁹ See Scheineson and Cuevas, 68 Food & Drug L J at 211 (cited in note 28); Marcia M. Boumil and Kaitlyn L. Dunn, *Off-Label Marketing of Pharmaceutical Products in the Wake of United States v. Caronia and United States v. Harkonen*, 9 J Health & Biomedical L 385, 430–31 (2014) (noting some of the ways in which the government’s approach to arguing off-label claims might change in the wake of *Caronia*).

¹⁰⁰ See, for example, Complaint, *United States v Shire Specialty Pharmaceuticals*, Civil Action No 08-4795, *8 (ED Pa filed Oct 7, 2008) (“Shire Specialty Complaint”). See also Third Amended Complaint, *United States v Bayer Corp*, Civil Action No 05-3895, *22–23 (D NJ filed Mar 1, 2010); Complaint, *United States v Janssen Pharmaceutical Products LP*, Civil Action No 04-cv-1529, *11, 18–21 (ED Pa filed Nov 4, 2013). For industry commentary about the relationship between *Caronia* and false or misleading accusations, see Michael Rogoff, Manvin Mayell, and Paula Ramer, *The Aftermath of Caronia in Pursuing Off-Label Cases* (InsideCounsel, Mar 10, 2014), archived at <http://perma.cc/92QE-AHPR>.

¹⁰¹ See Scheineson and Cuevas, 68 Food & Drug L J at 205–06, 211 (cited in note 28).

¹⁰² See *In re Neurontin Marketing and Sales Practice Litigation*, 712 F3d 21, 27–28 (1st Cir 2013).

¹⁰³ 134 S Ct 2228 (2014).

preclude suits for false or misleading advertising under other statutes.¹⁰⁴ This decision eliminated a substantial source of legal uncertainty for prospective plaintiffs and is likely to encourage private-party suits in the future.

A number of statutes provide for such causes of action. Notably, the recent First Circuit decision in *In re Neurontin Marketing and Sales Practice Litigation*¹⁰⁵ demonstrated that the Racketeer Influenced and Corrupt Organizations Act¹⁰⁶ (RICO) can be a vehicle to seek damages for fraudulent off-label marketing.¹⁰⁷ The decision is an important precedent on how to apply RICO to off-label marketing, an issue that had been a source of considerable uncertainty.¹⁰⁸ Competitors of companies that engage in false or misleading off-label marketing can also seek damages for lost sales under the Lanham Act.¹⁰⁹ Finally, private parties with information about false or misleading off-label marketing—including drug-company employees—may assist the government in pursuing claims through the *qui tam* provisions of the False Claims Act.¹¹⁰ In light of the increased incentives for private parties to bring claims since *POM Wonderful*, developing a clear test for whether off-label promotion is false or misleading is more important than ever.

¹⁰⁴ *Id.* at 2233.

¹⁰⁵ 712 F3d 21 (1st Cir 2013).

¹⁰⁶ 18 USC § 1961 et seq.

¹⁰⁷ *In re Neurontin*, 712 F3d at 25–27.

¹⁰⁸ See J. Gordon Cooney Jr, John P. Lavelle Jr, and Bahar Shariati, *Back to the Future: Civil RICO in Off-Label Promotion Litigation*, 77 *Defense Counsel J* 168, 169–70 (2010) (discussing the wide variety of ways in which courts previously resisted the application of RICO to off-label marketing).

¹⁰⁹ See 15 USC § 1051 et seq. See also generally, for example, *Zeneca Inc v Eli Lilly and Co*, 1999 WL 509471 (SDNY). Examples of such cases are rare, because it was unclear whether such suits were precluded prior to *POM Wonderful*.

¹¹⁰ 31 USC § 3729 et seq. For an example of such a suit, see Shire Specialty Complaint at *14–15 (cited in note 100). The case settled in September 2014. See Press Release, *Shire Pharmaceuticals LLC to Pay \$56.5 Million to Resolve False Claims Act Allegations Relating to Drug Marketing and Promotion Practices* (US Department of Justice, Sept 24, 2014), archived at <http://perma.cc/3UYX-4TFU>. See also Michelle M. Mello, David M. Studdert, and Troyen A. Brennan, *Shifting Terrain in the Regulation of Off-Label Promotion of Pharmaceuticals*, 360 *New Eng J Med* 1557, 1561 (2009) (describing the use of the False Claims Act to seek damages for economic harm caused by off-label promotion).

II. DEFINING “FALSE OR MISLEADING”

Though claims of false or misleading off-label marketing are likely to increase, there is no single, working definition of the term. In the FDCA context, courts have rarely addressed the issue because the dominant assumption of per se unlawfulness had rendered such a definition unimportant.¹¹¹ Extrajudicial sources of information do not provide useful guidance either.¹¹² The FDA has not advanced a definition of “false or misleading” for the off-label context. Though the FDA has promulgated regulations describing the characteristics of false or misleading on-label marketing,¹¹³ these regulations are not, on their own, sufficient to address off-label marketing. In one sense, their guidance is too general for the off-label context: the regulations for on-label marketing involve advertising to the lay audience, whereas physicians are the relevant audience for off-label marketing.¹¹⁴ In another sense, the guidance is too specific: it relates only to claims about studies and uses that have received FDA approval, as opposed to those that have not. Moreover, these regulations seem to conflict somewhat with the few examples of false or misleading off-label claims that are described in the FDA’s guidance on proper scientific exchange.¹¹⁵ Thus, the agency’s position is far from certain.

Nor have litigants (including the government) agreed on a precise definition of “false or misleading” under other statutes.

¹¹¹ When courts have addressed off-label marketing in the non-FDCA context, the typical fact pattern has involved such blatant data falsification or premeditated fraud that little in-depth analysis has been required. See, for example, *In re Neurontin*, 712 F3d at 28 (finding that Pfizer sponsored “misleading informational supplement and continuing medical education” courses and suppressed “negative information about Neurontin while publishing articles in medical journals that reported positive information”); *United States v Harkonen*, 510 Fed Appx 633, 636 (9th Cir 2013) (noting that the defendant stated that he would “cut that data and slice it until [he] got the kind of results [he was] looking for”).

¹¹² Even the academic literature has not reached a consensus. Some commentators have recognized that establishing a standard of truthfulness is likely to be an important issue in the future but have generally focused on developing arguments for upholding an off-label ban. See, for example, Greenwood, 37 *Am J L & Med* at 280, 291 (cited in note 27); Elissa Phillip, *United States v. Caronia: How True Does “Truthful” Have to Be?*, 67 *Vand L Rev En Banc* 157, 166–69 (2014).

¹¹³ 21 CFR § 202.1(e)(6)–(7) (listing behaviors that constitute “false or misleading” advertising, such as mischaracterizing the results of drug studies or overstating the safety of a given drug).

¹¹⁴ See Parts II.B, III.C.

¹¹⁵ While the advertising regulations simply require that advertising speech be truthful and nonmisleading, the standard for scientific exchange seems to be higher. See text accompanying notes 53–65.

Briefs and settlement agreements typically state that the relevant drug marketing was false or misleading without specifically describing what aspect of the claims establishes that fact.¹¹⁶ Because most cases have proceeded under the qui tam provision of the False Claims Act and have ended in settlement,¹¹⁷ there are few detailed evaluations of whether off-label speech is false or misleading. Further, complainants' briefs are the only detailed exposition of the law and facts in such cases, and they provide only a partial and biased representation of how the law might be interpreted.¹¹⁸

However, the courts have developed a definition of the term "false or misleading" for the commercial-advertising context under two federal false advertising statutes: the Lanham Act and the FTC Act (the "false advertising statutes"). This Part argues that the definition of "false or misleading" developed in the case law associated with the false advertising statutes should be applied to the definition of "false or misleading" in the off-label-promotion context. Section A provides a brief overview of the false advertising framework. Section B demonstrates that this existing "false or misleading" definition is also appropriate for the FDCA context.

A. "False or Misleading" under the False Advertising Statutes

Two federal statutes prohibit false or misleading advertising and promotion: the Lanham Act and the FTC Act. The Lanham Act gives competitors standing to sue for false advertising,¹¹⁹ while the FTC Act establishes the FTC and gives the Commission the authority to prosecute false advertising claims.¹²⁰ Though the statutes differ in terms of legal purpose—the Lanham Act protects competitors against unfair competition, while the FTC Act prevents consumer deception—the definition of "false or misleading" consists of essentially the same elements under both statutes. Specifically, a court must find that the

¹¹⁶ See, for example, GSK Complaint at *7, 41 (cited in note 1); GSK Settlement at *3–5 (cited in note 3).

¹¹⁷ See 31 USC § 3730(b).

¹¹⁸ Because the government does not accord *Chevron* deference to agency positions advanced in litigation, the government's briefs do not necessarily reflect how courts would likely resolve these cases. See Cass R. Sunstein, *Chevron Step Zero*, 92 Va L Rev 187, 214–15 (2006).

¹¹⁹ See 15 USC § 1125(a).

¹²⁰ See 15 USC § 41; 15 USC § 53(a).

advertisement is likely to mislead a reasonable consumer in a material way.¹²¹

To determine whether an advertisement is deceptive under the false advertising statutes, courts first consider the advertisement from the perspective of a reasonable member of the audience for a drug advertisement.¹²² If the reasonable audience member would take material action based on the advertisement, courts compare this material action to what is justified based on an objective analysis of all the facts known to the producer of the product.¹²³ An advertisement is an actionable misrepresentation if a reasonable audience member’s reaction differs from what would otherwise be justified by the complete information.¹²⁴

B. “False or Misleading” under the FDCA

Policing off-label speech presents analogous challenges to those presented in false advertising cases. Off-label speech, like advertising, is commercial and self-interested in nature. And off-label speech, like advertising, can generate enormous value for consumers. In both contexts, an appropriate definition of false or misleading speech must balance the public’s competing interests in consumer and competitor protection on the one hand and the dissemination of useful information on the other.

Given these parallels, it seems natural that courts considering off-label marketing cases in the Lanham Act context would

¹²¹ The FTC clarified this definition in a 1983 Policy Statement. See *FTC Policy Statement on Deception* (Federal Trade Commission, Oct 14, 1983), archived at <http://perma.cc/6WW2-TY3H>. Courts apply a similar formulation under the Lanham Act. See, for example, *Sandoz Pharmaceuticals Corp v Richardson-Vicks, Inc*, 902 F2d 222, 231 (3d Cir 1990) (“A Lanham Act plaintiff must prove, by a preponderance of the evidence, (1) that the defendant’s promotions contained a material representation or description, and (2) that this material representation or description was false or verifiably misleading.”).

¹²² See *In the Matter of Thompson Medical Co*, 104 FTC 648, 688 (1984). Courts applying the Lanham Act generally require extrinsic evidence of consumer decisions. See, for example, *American Council of Certified Podiatric Physicians and Surgeons v American Board of Podiatric Surgery, Inc*, 185 F3d 606, 613 (6th Cir 1999); *McNeil-PPC, Inc v Pfizer Inc*, 351 F Supp 2d 226, 249 (SDNY 2005). Courts applying the FTC Act do not always require extrinsic evidence, determining in some cases that “the FTC’s unique expertise and experience regarding consumer expectations allows it to determine for itself the level of substantiation consumers expect to support an advertising claim.” *Sandoz Pharmaceuticals Corp*, 902 F2d at 229. See also *Thompson Medical Co v Federal Trade Commission*, 791 F2d 189, 196 (DC Cir 1986).

¹²³ See *Federal Trade Commission v Cyberspace.com, LLC*, 453 F3d 1196, 1201 (9th Cir 2006).

¹²⁴ See *id.*; *Thompson Medical Co*, 791 F2d at 197.

apply the usual framework to assess whether competitors are entitled to redress for false or misleading off-label claims. But it is not immediately clear that the same can be said for the government's consumer-protection suits brought under the FDCA. The FDCA prohibits false or misleading speech about prescription drugs because such speech can lead doctors to prescribe drugs that are unsafe or ineffective.¹²⁵ Unlike in the Lanham Act context, the focus of lawsuits brought under the FDCA is to ensure public health and safety. Thus, the key question for courts determining whether to apply the false advertising framework to off-label speech is whether the likelihood that a reasonable physician will be materially misled by an off-label claim is a reliable metric for distinguishing between speech that creates such safety risks and speech that may advance the state of medical science.¹²⁶ This Section demonstrates that a definition of "false or misleading" that is predicated on physician judgment is consistent with the FDCA's goal of ensuring drug safety and effectiveness.

1. The FDCA defines drug "safety and effectiveness" in relative, not absolute terms.

Drug safety and effectiveness are not self-defining concepts. As the clinical trial process illustrates, "safe and effective" in the FDCA context refers to a level of confidence about underlying scientific facts that is sufficient to warrant FDA approval of a new drug.¹²⁷ Federal regulations require drug companies to conduct an elaborate series of "well-controlled" clinical trials to generate comprehensive data about drug safety and effectiveness.¹²⁸ The first two phases of clinical trials are centered on generating data on drug toxicity and side effects; the FDA gives limited weight to the effectiveness question until the third phase of

¹²⁵ See Henry A. Waxman, *A History of Adverse Drug Experiences: Congress Had Ample Evidence to Support Restrictions on the Promotion of Prescription Drugs*, 58 *Food & Drug L J* 299, 300–01 (2003). The centrality of drug safety and efficacy is the dominant theme of the FDA's drug-advertising regulations. See, for example, 21 CFR § 202.1(e).

¹²⁶ See Part I.B.3.

¹²⁷ See notes 18–24 and accompanying text.

¹²⁸ See 21 USC § 355(d) (requiring drugmakers to provide "data from [an] adequate and well-controlled clinical investigation and confirmatory evidence" to demonstrate that drugs proposed for FDA approval are effective); 21 CFR § 314.126(a) (specifying requirements that clinical investigations must satisfy to be considered "adequate and well-controlled"). See also *Drug Development and Review Definitions* (cited in note 17).

trials, when a drug has already passed these threshold tests.¹²⁹ Before each trial stage, the drugmaker and the FDA select metrics¹³⁰ (called endpoints) that are probative of the drug’s risks and benefits.¹³¹ The relevant endpoints vary by drug, based on what measurements the FDA and drugmaker deem appropriate for the particular uses and patient populations being studied.¹³²

It is important to distinguish the measurements of drug safety and effectiveness obtained in clinical trials from the legal definition of “safe and effective.” Though the FDCA sets forth a highly structured framework for measuring safety and effectiveness, neither the statute’s text nor its regulations establish a uniform standard for what constitutes a “safe” or “effective” drug. Rather, the legal definition of “safe and effective” invokes the overall risk-benefit profile of the drug—whether the benefits that the drug promises justify the risks that it poses to patients.¹³³

2. Safety and effectiveness are a matter of physician judgment.

Though the FDCA charges the FDA with the task of ensuring that a new drug possesses a favorable balance of risks and benefits for at least one clinical use,¹³⁴ the statute otherwise explicitly reserves to physicians the task of weighing drug risks and benefits when recommending prescriptions to their patients.¹³⁵ The FDCA states that it does not “limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed [drug] for any condition or disease within a legitimate health care practitioner-patient relationship.”¹³⁶ As the Supreme

¹²⁹ See *Drug Development and Review Definitions* (cited in note 17). The three-stage process consists of Phase I studies that establish that the drug is nontoxic in healthy volunteers; Phase II studies that generate preliminary data on drug effectiveness and demonstrate the drug’s clinical characteristics, such as side effects; and Phase III studies that provide comprehensive safety-effectiveness data in a realistic patient population. See *id.*

¹³⁰ 21 USC § 355(b)(5)(B) (providing that NDA applicants may make “a reasonable written request for a meeting [with the FDA] for the purpose of reaching agreement on the design and size of clinical trials”).

¹³¹ See *Drug Development and Review Definitions* (cited in note 17).

¹³² See 21 USC § 355(b)(5)(B).

¹³³ See 21 USC § 355(d) (providing that FDA officials shall determine whether a drug is sufficiently safe and effective by “implement[ing] a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks”).

¹³⁴ See 21 USC § 355(d).

¹³⁵ See 21 USC § 396.

¹³⁶ 21 USC § 396.

Court has held, the primacy of physician judgment extends to off-label uses.¹³⁷ The Supreme Court and lower courts have further affirmed that physicians retain the power to make prescribing decisions even though drug companies or patients might seek to influence those decisions.¹³⁸

The FDA's gatekeeping authority under the premarket-approval system is best understood, then, as a limited exception to the general rule that physicians are free to prescribe whatever drug they deem appropriate for a particular patient. The history of drug regulation confirms that the premarket-approval process is a pragmatic concession to the realities of the drug market. Prior to the FDCA's Drug Amendments of 1962,¹³⁹ which established the modern premarket-review and clinical trial processes,¹⁴⁰ the lack of entry barriers to the drug market led to rampant false or misleading promotion.¹⁴¹ The sheer volume of misleading drug claims made it difficult for busy doctors to evaluate which drugs were safe and effective for particular uses.¹⁴² This problem was compounded by the fact that early twentieth-century medical training—unlike medical training today¹⁴³—did not provide most doctors with the analytical skills required to track down and evaluate data about new drug products.¹⁴⁴ As a result, doctors were often forced to engage in

¹³⁷ *Buckman Co v Plaintiffs' Legal Committee*, 531 US 341, 350 (2001) (“[O]ff-label usage . . . is an accepted and necessary corollary of the FDA’s mission to regulate in this area without directly interfering with the practice of medicine.”).

¹³⁸ See notes 75–96 and accompanying text. The Supreme Court has expressed skepticism over the idea that physicians would allow marketing or patient requests for a drug to adversely affect their professional judgment. Thus, the Court would be unlikely to uphold restrictions on off-label marketing (which drug companies generally communicate specifically to physicians), even if the public did become aware of drug companies’ claims. See *Virginia State Board of Pharmacy v Virginia Citizens Consumer Council, Inc.*, 425 US 748, 766–69 (1976).

¹³⁹ Pub L No 87-781, 76 Stat 780, codified as amended at 21 USC § 301 et seq.

¹⁴⁰ See Drug Amendments of 1962, § 102(c), 76 Stat at 781, codified at 21 USC § 355 (requiring drug manufacturers to demonstrate drug safety and efficacy by “substantial 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 involved”). See also 21 USC § 355(d).

¹⁴¹ See Waxman, 58 Food & Drug L J at 300–04 (cited in note 125).

¹⁴² See *id.* at 301–03.

¹⁴³ See Maria A. Blanco, et al, *A Survey Study of Evidence-Based Medicine Training in US and Canadian Medical Schools*, 102 J Med Library Assoc 160, 163 (2014) (listing examples of modern evidence-based-medicine tools used to formally train medical students).

¹⁴⁴ See *Drug Industry Act of 1962*, S Rep No 87-1744, 87th Cong, 2d Sess 37 (1962), reprinted in 1962 USCCAN 2884, 2902 (“Leading physicians testified that it is impossible

guesswork, which led them to prescribe harmful or ineffective drugs.¹⁴⁵ Congress instituted the premarket-approval process to control this deluge of false and misleading claims and to ensure that physicians would have a sound factual basis for evaluating a drug’s risks and benefits.

The introduction of the structured clinical trial process decreased the volume of spurious claims by permitting drugmakers to market only those substances that had been proven safe and effective for a clinical use.¹⁴⁶ As a result, the risks of off-label prescribing are significantly lower today than they were in the past. Any drug that is the subject of off-label marketing has, by definition, already been deemed safe through the clinical trial process—so only drug effectiveness is at stake in off-label cases.¹⁴⁷ Moreover, the consolidation of the pharmaceutical industry since the Drug Amendments of 1962 has decreased the incentives for false or misleading promotion: unlike the numerous small operations of the mid-twentieth century,¹⁴⁸ today’s drug companies are repeat players with reputations to protect.¹⁴⁹

Thus, the clinical trial and regulatory processes ease physicians’ assessments of drug risks and benefits in two ways. First, the clinical trial process ensures that all drugs come with a comprehensive safety profile that details what tests have and have not been done, in addition to the results of those tests. Second, the process cabins the drug market to only those drugs proven to have positive health effects that justify their risks, ensuring that drug companies cannot market inert substances as efficacious cures. These limitations—though they do reduce the number of drugs that doctors can prescribe—ensure that physicians have information of sufficient quantity and quality to exercise their professional judgment in making off-label prescribing

to keep currently informed of the state of medical knowledge to be found scattered in hundreds of medical journals on the 400 new drugs introduced each year.”).

¹⁴⁵ See *id.*

¹⁴⁶ See Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 Va L Rev 1753, 1764–66 (1996).

¹⁴⁷ See notes 18–24 and accompanying text.

¹⁴⁸ See *Drug Industry Antitrust Act, Hearings before the Antitrust Subcommittee (Subcommittee No 5) of the Committee on the Judiciary on HR 6245*, 87th Cong, 2d Sess 212 (1962) (“1962 Drug Industry Hearings”) (statement of Dr. Martin Cherkasky) (discussing the role of mid-twentieth-century “detailmen”—individual drug advertisers who provided physicians with various promotional materials).

¹⁴⁹ See Howard Bauchner and Phil B. Fontanarosa, *Restoring Confidence in the Pharmaceutical Industry*, 309 JAMA 607, 607 (2013) (describing the various reputational concerns of large pharmaceutical companies today).

decisions. In this way, the regulatory system supports and preserves the FDCA's commitment to physician primacy in making judgments about safety and effectiveness.

3. Speech is false or misleading if it undermines physicians' judgments about safety and effectiveness.

The centrality of physician judgment to pharmaceutical regulation is evident from Congress's decision to preserve physician discretion, even as it instituted the clinical trial process as a gold standard for substantiating drug claims.¹⁵⁰ To the extent practicable, the regulatory regime is designed to allow physicians to make the ultimate judgment about whether a drug's risk-benefit profile is suitable for a given patient.¹⁵¹ In other words, a drug is "safe and effective" for a patient if a physician, in her professional judgment, says that it is.

Since physicians are responsible for deciding which drugs to prescribe, theirs is the relevant judgment to consider when determining whether an off-label marketing claim makes false or misleading statements about safety and effectiveness.¹⁵² A physician's ability to decide which drugs are safe and effective improves if she is provided with true and nonmisleading information. Conversely, speech that is false or misleading impedes a physician's ability to make such decisions, causing physicians to prescribe unsafe or ineffective drugs.

III. ADOPTING THE FALSE ADVERTISING STATUTES' DEFINITION OF "FALSE OR MISLEADING" FOR OFF-LABEL MARKETING

As the preceding discussion demonstrates, false or misleading off-label speech compromises patient health and safety only if it interferes with physicians' prescribing decisions. Thus, the effect of off-label speech on physicians' ability to make informed prescribing decisions is an appropriate metric for distinguishing false or misleading off-label speech from potentially valuable communication. The analogy to the false advertising framework

¹⁵⁰ See Klasmeier and Redish, 37 Am J L & Med at 323 (cited in note 25).

¹⁵¹ See *id.*

¹⁵² Note that this is true even though information about off-label uses makes its way into the popular media. See notes 189–92 and accompanying text. See also *Benrus Watch Co v Federal Trade Commission*, 352 F2d 313, 319–20 (8th Cir 1965) (determining that, when the buyer of a product is not a member of the product's targeted audience, the buyer's reasonable perception of advertisements for the product nevertheless determines whether the advertisement was unlawfully deceptive).

is clear. Under the false advertising statutes, an advertising claim is false or misleading if it causes a reasonable consumer to make a different purchasing decision than she would otherwise have made in the face of complete and accurate information about the advertised product.¹⁵³ Similarly, an off-label statement is false or misleading if it leads a reasonable physician to make a different prescribing decision than she would otherwise have made in the face of complete and accurate information about the promoted prescription drug.

Because this metric for evaluating off-label speech is so closely related to that used in the well-established false advertising framework, this Part argues that courts should adopt the approach used for the false advertising statutes as a universal framework for identifying false or misleading off-label speech. Section A describes the practical benefits of adopting this approach: the deployment of a familiar and tested framework for evaluating health claims, and the establishment of a consistent definition across statutory contexts. Section B explains how the false advertising approach would give drug companies incentives not only to minimize false or misleading off-label speech but also to maximize dissemination of truthful off-label speech. Finally, Section C describes how courts should adapt and apply the approach in the off-label marketing context.

A. Practical Benefits of the False Advertising Framework

1. The false advertising approach is a tested framework for evaluating health claims.

The false advertising statutes’ unfair-and-deceptive-advertising provisions are a tested approach to identifying false or misleading drug claims. The FTC has regulated false advertising of nonprescription drugs and supplements by applying this framework under the FTC Act for over seventy-five years.¹⁵⁴ In fact, the FTC long regulated prescription drug advertisements as

¹⁵³ See *Federal Trade Commission v Cyberspace.com LLC*, 453 F3d 1196, 1199–1200 (9th Cir 2006).

¹⁵⁴ See Act of Mar 21, 1938, 52 Stat 111, 114, codified as amended at 15 USC § 52(a) (giving the FTC the authority to regulate advertising). Under these provisions, the FTC has some responsibilities in enforcing the Lanham Act’s advertising provisions; courts applying the Lanham Act use a virtually identical framework.

well.¹⁵⁵ During the 1920s and 1930s, more than half the FTC's workload consisted of policing false or misleading drug-, device-, and cosmetic-related claims.¹⁵⁶

Though the regulation of prescription drugs migrated to the FDA over time, this development is best seen as the result of the FDA's effort to maintain the integrity of its regulatory process, rather than a judgment about the sufficiency of the FTC framework as a method for identifying false or misleading drug claims. Perhaps most tellingly, Congress never transferred jurisdiction over prescription drug advertising from the FTC. In fact, Congress explicitly declined to do so: prior to passing the FDCA, the FDA engaged in an energetic lobbying campaign to gain jurisdiction over false advertising in this area, but Congress refused to transfer authority to the agency.¹⁵⁷ A variety of cases and administrative adjudications from the years following the FDCA's passage show that the three branches of government viewed the FTC's jurisdiction over false advertising as exclusive.¹⁵⁸ In the ensuing years, the FDA circumvented this limitation on its authority by interpreting its authority over the NDA and labeling processes as authority to prosecute drug companies for advertisements that tend to undermine the regulatory process.¹⁵⁹ As a result, the FDA now exercises authority over prescription drug promotion.

Even as the FDA obtained control over and experience with regulating drug promotion, the FTC has maintained unbroken authority over nonprescription drugs and medical devices. The FTC has regularly applied the false advertising regulations to health claims related to nutritional supplements and over-the-counter drugs.¹⁶⁰ That Congress has not transferred regulatory authority over the advertising of these items to the FDA—despite the agency's subject matter expertise and growing experience regulating advertising—demonstrates the success of the

¹⁵⁵ See Terry S. Coleman, *Origins of the Prohibition against Off-Label Promotion*, 69 Food & Drug L J 161, 168 (2014).

¹⁵⁶ See *id.*

¹⁵⁷ See *id.* at 175–76.

¹⁵⁸ See *id.* at 180–81, 194.

¹⁵⁹ See Coleman, 69 Food & Drug L J at 178–93 (cited in note 155).

¹⁶⁰ See, for example, *In the Matter of Body Wise International, Inc.*, 120 FTC 704, 725–28 (1995) (applying the FTC Act to a claim alleging false advertising of various nutritional supplements); *In the Matter of Thompson Medical Co.*, 104 FTC 648, 783–86 (1984) (applying the FTC Act to a claim alleging false advertising of the over-the-counter drug Aspercreme).

FTC framework in balancing the public’s competing interests in consumer protection and the dissemination of useful information in the sensitive area of human health.¹⁶¹

2. The definition of “false or misleading” off-label speech should be uniform under all statutes.

Courts should adopt the false advertising statutes’ definition of “false or misleading” in the FDCA context in order to ensure a uniform definition of the term among the various statutory contexts that provide potential causes of action for false or misleading off-label claims. Of the statutes that can give rise to claims related to false or misleading off-label marketing, only the Lanham Act—under which courts have adopted the same framework as under the FTC Act—has a detailed framework for identifying false or misleading promotion.¹⁶² Because, as noted above, this is both congressionally endorsed and a well-established approach to evaluating health claims for nonprescription drugs, courts will likely extend this framework to Lanham Act claims related to the off-label marketing of prescription drugs.

This false advertising framework is also likely to be a default framework for other statutes that provide causes of action to redress financial harms caused by fraud more generally. Though different plaintiffs will be eligible to pursue actions under different statutes, the mechanism of harm—interference with physician judgment—is the same for all prospective complainants. For example, reimbursement agencies seeking redress through RICO can prove causation only by demonstrating that a drugmaker’s false or misleading claim actually led physicians to prescribe a more expensive drug than they otherwise

¹⁶¹ See Beales, 24 Seton Hall L Rev at 1380–81 (cited in note 54). Though off-label claims admittedly require more-advanced technical analysis than a typical advertising claim, the Supreme Court’s decision in *Daubert v Merrell Dow Pharmaceuticals, Inc.*, 509 US 579 (1993), suggests that courts are capable of making judgments about the reliability of scientific evidence and determining whether such evidence is probative of a particular factual assertion. In *Daubert*, the Supreme Court noted that “federal judges possess the capacity” to assess whether scientific “reasoning or methodology . . . is scientifically valid and [] whether that reasoning or methodology properly can be applied to the facts” of the case. *Id.* at 592–93.

¹⁶² See Part II.A. Because the FDA, rather than the FTC, brings claims related to consumer protection in the prescription drug context, one would not expect to see FTC Act claims related to off-label marketing.

would have.¹⁶³ The government would need to make a similar showing to successfully argue that a drug company defrauded the Medicaid or Medicare system under the False Claims Act.¹⁶⁴ Because the false advertising framework is specifically designed to guide the assessment of whether a reasonable prescriber was materially misled by a promotional claim,¹⁶⁵ it is an ideal rule for identifying fraud in the off-label marketing context.

Given that the false advertising framework will likely be used to identify false or misleading speech under other statutes, the government should promote uniformity by adopting the same definition under the FDCA. A uniform definition of “false or misleading” is desirable because plaintiffs might bring claims under multiple statutes concurrently. For example, the DOJ might wish to simultaneously bring claims for false or misleading speech under the FDCA *and* the False Claims Act. A uniform definition of false or misleading speech under both causes of action would streamline litigation and reduce legal costs for both the plaintiff and the defendant. Further, given that the bad act (false or misleading speech), harm (wrong drug prescribed in reliance on false or misleading speech), and burden of proof are identical under each statute, adopting identical frameworks could allow parties to invoke collateral estoppel.¹⁶⁶ This would both discourage frivolous claims and encourage parties injured by off-label speech to engage in follow-on litigation, increasing the costs of false or misleading off-label marketing.

B. Normative Benefits of the False Advertising Framework

An ideal off-label marketing statute would both encourage drug companies to generate and deploy socially valuable information and discourage them from disseminating false or misleading information. The false advertising statutes achieve this balance through a burden-shifting framework. Under the statutes, a

¹⁶³ See *In re Neurontin*, 712 F3d at 39–41 (finding both proximate and but-for causation satisfied under RICO when the defendant-drugmaker had fraudulently induced physicians to prescribe Neurontin for an off-label use in higher quantities than they otherwise would have).

¹⁶⁴ See *United States v Aventis Pharmaceuticals, Inc.*, 512 F Supp 2d 1158, 1163 (ND Ill 2007).

¹⁶⁵ See *McNeil-PPC, Inc v Pfizer Inc*, 351 F Supp 2d 226, 248 (SDNY 2005) (requiring the plaintiff, in a case alleging false advertising under the Lanham Act, to demonstrate that the advertisements had been materially misleading to consumers).

¹⁶⁶ See M. Stuart Madden, *Issue Preclusion in Products Liability*, 11 Pace L Rev 87, 96–99 (1990).

plaintiff bears the initial burden of proving that an advertiser has made statements that elicit a material reaction from a reasonable audience member.¹⁶⁷ Meeting this burden requires the government to present “substantial evidence” that an advertisement, if unsubstantiated, is misleading.¹⁶⁸ However, advertisers themselves are responsible for substantiating their claims, either to the level of certainty claimed in the advertisement or, if no claim is stated explicitly, to an appropriate level given the breadth of the claim.¹⁶⁹ Since advertisers have already generated the data that substantiate their claims,¹⁷⁰ this scheme lowers litigation costs relative to a scenario in which the plaintiff bears the exclusive burden of proof.¹⁷¹

As a practical matter, giving drug companies the burden of substantiating their off-label claims would both deter deceptive off-label marketing and promote truthful off-label marketing more effectively than placing the burden of proof exclusively on the plaintiff.¹⁷² Under an arbitrary effectiveness standard (including a per se ban), a drug company’s decision to assert a claim is a function of the expected value of making the claim in terms of increased prescriptions, discounted by the likelihood of

¹⁶⁷ For cases describing the burden of proof under the Lanham Act, see *Pizza Hut, Inc v Papa John’s International, Inc*, 227 F3d 489, 495 (5th Cir 2000); *American Council of Certified Podiatric Physicians and Surgeons v American Board of Podiatric Surgery, Inc*, 185 F3d 606, 614 (6th Cir 1999); *Johnson & Johnson * Merck Consumer Pharmaceuticals Co v Smithkline Beecham Corp*, 960 F2d 294, 299 (2d Cir 1992). For a case describing the burden of proof under the FTC Act, see *Thompson Medical*, 104 FTC at 818 (“[T]he Commission has the burden of showing that the material claims communicated to reasonable consumers by the advertising are false in some manner.”).

¹⁶⁸ *Removatron International Corp v Federal Trade Commission*, 884 F2d 1489, 1497 (1st Cir 1989).

¹⁶⁹ See *id* at 1492 n 3. See also *McNeil-PPC*, 351 F Supp 2d at 250–51; *American Home Products Corp v Federal Trade Commission*, 695 F2d 681, 692–98 (3d Cir 1982).

¹⁷⁰ See *FTC Policy Statement regarding Advertising Substantiation* (Federal Trade Commission, Mar 11, 1983), archived at <http://perma.cc/75AP-FBRR>.

¹⁷¹ See Richard S. Higgins and Fred S. McChesney, *Truth and Consequences: The Federal Trade Commission’s Ad Substantiation Program*, 6 Intl Rev L & Econ 151, 153 (1986) (discussing how standards of proof affect information-gathering costs in litigation). Importantly, it seems unlikely that this lower burden of proof would lead to significantly more litigation. If an advertising claim is found to be misleading or nonmisleading for a particular population of physicians, then presumably estoppel would apply to future allegations about the same advertising claim.

¹⁷² See *id* at 157–58 (finding that shifting the burden of proof onto drug companies enabled the FTC “to challenge the accuracy of more [advertising] claims per budgetary dollar”).

an enforcement action.¹⁷³ Assuming that the likelihood of an enforcement action does not depend on the veracity of the drug claims (because the ban applies to any claims related to off-label marketing, whether true or false), drug companies are encouraged to design claims that will maximize the number of new prescriptions—a goal that is not necessarily aligned with patient interests. By contrast, the false advertising statutes’ framework makes patient interests an inherent part of the expected value of an off-label campaign. Because the likelihood of an enforcement action is directly related to the veracity of the claims, a drug company could minimize the enforcement “discount” of an off-label campaign by making only truthful, nonmisleading claims.

The incentive for drug companies to police their off-label communications for false or misleading speech is an important feature of the false advertising approach. Because drug marketing often takes place in private, outside the view of FDA regulators, misleading claims can be difficult for the agency to detect.¹⁷⁴ Moreover, there can be a substantial delay before practitioners recognize the misleading nature of a drug claim during the time when evidence about safety and effectiveness is accumulating.¹⁷⁵ By setting appropriate ex ante incentives, the false advertising approach ensures that patients can access valuable off-label information without an enhanced risk of receiving false or misleading information, relative to the current per se ban.

Importantly, the flexibility of the false advertising approach should not be confused with the uncertainty that prevails under the current scientific-exchange framework.¹⁷⁶ The false advertising approach, though flexible with respect to the range of potentially

¹⁷³ See Gary S. Becker and Kevin M. Murphy, *A Simple Theory of Advertising as a Good or Bad*, 108 Q J Econ 941, 945 (1993) (explaining why a producer’s advertising output is in part a function of advertising costs and expected returns on revenue).

¹⁷⁴ See Aaron S. Kesselheim, Michelle M. Mello, and David M. Studdert, *Strategies and Practices in Off-Label Marketing of Pharmaceuticals: A Retrospective Analysis of Whistleblower Complaints*, 8 PLOS Medicine 1, 2 (Apr 2011), archived at <http://perma.cc/VQ73-77DG>. For a historical perspective on the difficulties faced in identifying false advertising, see *1962 Drug Industry Hearings*, 87th Cong, 2d Sess at 214–15 (cited in note 148).

¹⁷⁵ See *1962 Drug Industry Hearings*, 87th Cong, 2d Sess at 173 (cited in note 148) (statement of Abraham Ribicoff, Secretary of Health, Education, and Welfare) (describing the delays and difficulties in obtaining research results to verify whether drug advertisements are false or misleading).

¹⁷⁶ See Part I.B.3.

acceptable studies and claims, provides a definite requirement: an off-label claim must be an accurate representation of the underlying data. In contrast, the high—and somewhat indefinite—standard for scientific exchange encourages drug companies to forgo opportunities to investigate new uses if the value of making claims about those uses does not exceed the cost of conducting studies that meet the expected high requirements.

Thus, the false advertising approach not only ensures that drug companies have reduced incentives to make false or misleading statements but also gives the companies sufficient incentives to generate useful information about off-label use.¹⁷⁷ Just as the strict substantiation requirement allows off-label research to drive drug claims, the desire to make off-label claims may drive the decision to conduct off-label research.¹⁷⁸ The precision of the false advertising approach thus minimizes the costs required to support off-label claims and maximizes the range of claims for which it is profitable to generate truthful and nonmisleading information.¹⁷⁹ This is important because drug companies’ decisions about whether to pursue drug research are ultimately informed by the monetary return on that research.¹⁸⁰ Research is profitable when it leads doctors to write prescriptions that generate revenues that exceed research costs.¹⁸¹ Under the false advertising approach, drug companies would be motivated to perform whatever amount of research is required to substantiate a valuable claim—that is, a claim that would prompt the population of reasonable physicians to write a profitable number of prescriptions.¹⁸² Since reasonable physicians will write only socially valuable prescriptions, pharmaceutical

¹⁷⁷ See Paul H. Rubin, *From Bad to Worse: Recent FDA Initiatives and Consumer Health*, in Richard T. Kaplar, ed., *Bad Prescription for the First Amendment: FDA Censorship of Drug Advertising and Promotion* 87, 88–90 (Media Institute 1993) (noting that drug companies have an incentive to make reliable, appropriately qualified claims about their products).

¹⁷⁸ See *id.*

¹⁷⁹ See Beales, 24 Seton Hall L Rev at 1381 (cited in note 54).

¹⁸⁰ See Anup Malani, Oliver Bombom, and Mark van der Laan, *Improving the FDA Approval Process* *2 (University of Chicago Law & Economics John M. Olin Working Paper No 580, Oct 2011), archived at <http://perma.cc/PBW6-5ZUL>.

¹⁸¹ See *id.*

¹⁸² See Charles J. Walsh and Alissa Pyrich, *FDA Efforts to Control the Flow of Information at Pharmaceutical Industry-Sponsored Medical Education Programs: A Regulatory Overdose*, 24 Seton Hall L Rev 1325, 1366 (1994). See also Malani, Bombom, and van der Laan, *Improving the FDA Approval Process* at *2 (cited in note 180).

companies have an incentive to generate socially valuable information about off-label uses.¹⁸³

C. Adapting and Applying the False Advertising Framework to Off-Label Marketing

As the preceding sections show, there are obvious practical and normative advantages to adopting the false advertising statutes' framework for identifying false or misleading speech in the context of off-label-marketing suits brought under other statutes. Through careful application of this framework, courts can ensure consumer protection without curtailing useful advertising. This Section describes how, specifically, courts should apply the framework in the off-label marketing context.

To find an advertisement false or misleading under the Lanham or FTC Acts, a court must be convinced that the advertisement misrepresents the facts in a way that is likely to materially mislead a reasonable consumer.¹⁸⁴ Generally, courts approach the analysis in three steps. First, the court defines a "reasonable consumer" for the advertisement. Then, the court asks whether that consumer would take material action based on the advertisement.¹⁸⁵ If the reasonable consumer would take material action based on the advertisement, then the court must finally determine whether the underlying advertisement is deceptive. If the advertisement is deceptive, then the claim is actionably misleading, because it fooled a reasonable consumer into acting on it.¹⁸⁶

Using GlaxoSmithKline's marketing of Wellbutrin as an illustrative example, the following sections describe how courts currently approach each of these steps and how this analysis could be adapted to the off-label-marketing context. The first section describes how courts characterize the "reasonable consumer" under the false advertising statutes, explains why the "reasonable physician" is the relevant consumer in the off-label marketing context, and highlights how courts might assess the reasonable physician's abilities and tendencies. The second

¹⁸³ See Malani, Bombom, and van der Laan, *Improving the FDA Approval Process* at *3–4 (cited in note 180).

¹⁸⁴ See *FTC Policy Statement on Deception* (cited in note 121). See also *Federal Trade Commission v Tashman*, 318 F3d 1273, 1277 (11th Cir 2003); *McNeil-PPC*, 351 F Supp 2d at 248.

¹⁸⁵ See *Cyberspace.com*, 453 F3d at 1201.

¹⁸⁶ See *id.*

section explains how courts evaluate materiality and illustrates how this approach could be adapted to determine whether physicians would make a material decision based on an off-label claim. The third section describes how courts discern whether a scientific claim is deceptive under the false advertising statutes and proposes specific inquiries for the off-label-marketing context.

1. Step one: defining the “reasonable consumer.”

Under the false advertising statutes, a statement cannot be deceptive unless, given all the circumstances, it is likely to mislead a reasonable member of the target audience for the advertisement.¹⁸⁷ To determine whether a statement meets these requirements, a court must first identify the characteristics of a reasonable audience member. Courts typically begin by determining which individuals comprise the target audience, based on the type of product being advertised.¹⁸⁸ Courts also consider the groups to which the advertising is targeted.¹⁸⁹ The targeted group is generally determined based on context,¹⁹⁰ but direct evidence of an advertiser’s intent may also be probative.¹⁹¹ Under the false advertising framework, when advertising is targeted toward only experts, their perception of the advertisement governs.¹⁹²

Applying these analyses to the prescription drug context is straightforward. Under the false advertising statutes, the relevant consumer is the individual who makes the decision about which product to consume, not the individual who ultimately uses the product.¹⁹³ In the prescription drug context, US law treats physicians as the decisionmakers. In nearly all US jurisdictions, doctors are considered “learned intermediaries” who are responsible for deciding which treatment options their patients should

¹⁸⁷ See *FTC Policy Statement on Deception* (cited in note 121). See also *Tashman*, 318 F3d at 1277.

¹⁸⁸ See, for example, *Benrus Watch Co v Federal Trade Commission*, 352 F2d 313, 319 (8th Cir 1965) (analyzing a claim alleging that certain watches were falsely advertised by considering the advertisements’ effects on watch purchasers).

¹⁸⁹ See, for example, *Koch v Federal Trade Commission*, 206 F2d 311, 316–18 (6th Cir 1953) (explaining the significance of the fact that allegedly misleading advertisements had been targeted at laypersons as well as members of the medical profession).

¹⁹⁰ See *id.*

¹⁹¹ See, for example, *In re Neurontin*, 712 F3d at 27–28 (summarizing a drugmaker’s internal documents demonstrating direct intent to market a pharmaceutical product to physicians and third-party payers).

¹⁹² See *Koch*, 206 F2d at 316.

¹⁹³ See H. Thomas Austern, *What Is “Unfair Advertising”?*, 26 Food, Drug, Cosmetic L J 659, 663 (1971).

pursue.¹⁹⁴ In the on-label context, these jurisdictions hold that drug manufacturers have a duty to warn only members of the medical profession about product risks, even though pharmaceutical companies may sometimes engage in direct-to-consumer advertising.¹⁹⁵ Because the law treats licensed medical professionals as responsible for making prescribing decisions, they are the only audience members who can take material action based on advertising claims. Applying this to the off-label context, the audience for an off-label claim should thus include any medical professional who makes prescribing decisions.¹⁹⁶ A court might choose to define the audience even more narrowly if the evidence suggests that a drug company directed its off-label claims toward particular classes of physicians.

After defining the target audience for a company's off-label marketing, the court would next characterize that audience in terms of the typical member's ability to weigh off-label-marketing claims. Relevant criteria in this context could include advanced training, whether the physicians' prescribing habits indicate familiarity and comfort with the standard of care for the illness at issue, and the extent to which treatment standards are evolving. For example, specialized medications like those used in oncology or psychiatry might be advertised to only a highly trained subset of physicians who are working on the cutting edge of medical science and regularly consider new treatments.

The facts of the Wellbutrin case illustrate how this two-part inquiry would work.¹⁹⁷ The government's complaint does not specify whether GlaxoSmithKline's marketing was directed toward particular groups of practitioners. This is unsurprising: it is in the complainant's interest to suggest an inclusive definition of the target audience for the off-label statements.¹⁹⁸ Had the

¹⁹⁴ Diane Schmauder Kane, *Construction and Application of Learned-Intermediary Doctrine*, 57 ALR5th § 2(a) at 29 (West 1998).

¹⁹⁵ See *id.* at § 2(a) at 26.

¹⁹⁶ See David M. Fritch, *Speak No Evil, Hear No Evil, Harm the Patient? Why the FDA Needs to Seek More, rather than Less, Speech from Drug Manufacturers on Off-Label Drug Treatments*, 9 Mich St J Med & L 315, 355 (2005) ("As long as the prescribing physician remains in charge of the 'purchase' decision for prescription drugs—the issue of whether scientific information regarding off-label uses of prescription drugs is misleading or not is properly focused on the prescribing physician.")

¹⁹⁷ See notes 1–9 and accompanying text.

¹⁹⁸ For an example of how audience composition influences the reasonableness analysis, see *Koch*, 206 F2d at 316–17 (setting forth different reasonableness standards depending on whether the targeted audience consisted of members of the medical profession or laypersons).

case progressed to trial, GlaxoSmithKline would likely have presented evidence demonstrating the sophistication of the physicians who received the pertinent off-label claims—for example, by presenting evidence that the firm invited only specialists to its seminars and sales calls.

Assuming that the United States had successfully argued that GlaxoSmithKline’s off-label claims were directed toward general practitioners as well as specialists—that is, all physicians—the court would next have examined the ability of general practitioners to weigh claims about Wellbutrin. The court would have noted that general practitioners commonly treat straightforward cases of depression and are familiar with the range of antidepressants that are substitutes for Wellbutrin. On the other hand, general practitioners habitually refer severe cases of depression to experts in psychiatry.¹⁹⁹ Thus, a reasonable member of the physician audience could be expected to consider off-label claims in the context of routine, low-risk cases but would be hesitant to implement innovative and risky new treatment options in more-severe cases. The court would have considered these tendencies and capabilities in its subsequent materiality analysis.

2. Step two: assessing materiality.

Once the audience for an advertising claim has been defined, a court must determine whether a reasonable member of that audience is likely to take a material action based on the allegedly misleading advertisement—that is, in this setting, to make a prescribing decision based on it.²⁰⁰ Under the FTC Act, a reasonable audience member’s interpretation of a claim could depend on factors such as the range of possible interpretations of the advertisement and the plausibility of those interpretations, the context in which the claims are made or transmitted,

¹⁹⁹ See E.S. Paykel and R.G. Priest, *Recognition and Management of Depression in General Practice: Consensus Statement*, 305 *Brit Med J* 1198, 1201–02 (1992); Harold E. Bronheim, et al, *The Academy of Psychosomatic Medicine Practice Guidelines for Psychiatric Consultation in the General Medical Setting*, 39 *Psychosomatics* S8, S12–13 (1998).

²⁰⁰ See *In the Matter of Heinz W. Kirchner*, 63 *FTC* 1282, 1290 (1963). See also *FTC Policy Statement on Deception* (cited in note 121).

and the overall presentation of the information.²⁰¹ Courts evaluate these factors in light of market realities.²⁰²

The market realities relevant to the materiality of off-label promotion can be divided into two broad categories. First, courts must consider the regulatory, legal, and factual context in which physicians receive off-label promotions. Second, courts must consider the conditions under which members of the relevant audience practice medicine: the kinds of cases to which the physicians might apply what they learn, and what other information is available to help them make prescribing decisions.²⁰³ The ensuing discussion considers how courts would assess each of these market realities in this context.

a) Regulatory, legal, and factual circumstances pertinent to materiality. In the off-label marketing context, the task of determining a reasonable physician's reaction to off-label marketing is complicated by the fact that the realities of pharmaceutical marketing will likely depend on how the FDA and courts treat off-label marketing in the future. Prior to the Second Circuit's decision in *Caronia*, courts presumed off-label marketing to be illegal.²⁰⁴ Nevertheless, one can infer from the damage estimates included in off-label-marketing settlement agreements—which are correlated with the number of prescriptions attributable to off-label marketing²⁰⁵—that off-label marketing campaigns influence many physicians' prescribing decisions.

It is not clear whether physicians' reactions to off-label promotions reflect their professional assessment of the risks and benefits of prescribing a particular drug for an off-label use, or whether physicians mistakenly believe that the drug companies'

²⁰¹ See *FTC Policy Statement on Deception* (cited in note 121).

²⁰² See *id.* (indicating that whether "market incentives place strong constraints on the likelihood of deception" may factor into the determination of whether an advertisement is likely to materially mislead a reasonable consumer).

²⁰³ See, for example, *Sandoz Pharmaceuticals Corp v Richardson-Vicks, Inc.*, 902 F.2d 222, 225 (3d Cir 1990) (considering whether pediatricians would find an advertisement for a children's cough syrup to be "misleading," given evidence proffered about pediatricians' training and medical practice).

²⁰⁴ See Part I.C.1.

²⁰⁵ See, for example, GSK Press Release (cited in note 3); Press Release, *Justice Department Announces Largest Health Care Fraud Settlement in Its History* (US Department of Justice, Sept 2, 2009), archived at <http://perma.cc/472Q-K4XG>; Press Release, *Eli Lilly and Company to Pay \$1.415 Billion to Resolve Allegations of Off-Label Promotion of Zyprexa* (US Department of Justice, Jan 15, 2009), archived at <http://perma.cc/UGJ5-X4HH>.

claims are FDA approved.²⁰⁶ In the latter case, the claims’ illegality likely contributes to physicians’ misconceptions—because off-label claims are illegal, physicians will likely expect that sales claims are either on label or reflect the results of a well-performed study that meets the requirements of the FDA’s scientific-exchange exception to the de facto ban on off-label marketing.²⁰⁷ If off-label marketing were presumptively legal, marketing claims would no longer benefit from this veneer of reliability. As a result, physicians would have more reason to doubt such claims, making it more difficult for a claim to meet the materiality requirement.²⁰⁸

Were false or misleading off-label promotion presumptively lawful, the scope and type of claim content would be the factors most relevant to assessing materiality. Physicians would be unlikely to interpret high-level, general claims as persuasive scientific evidence of safety and effectiveness. Thus, it is unlikely that such claims would meet the materiality requirement.²⁰⁹ On the other hand, promotional communications that purport to deliver scientific information would be much more likely to spur material action.²¹⁰

The facts of the GlaxoSmithKline case provide an illustrative example. A court would not interpret a drug representative’s claim that Wellbutrin is a “happy, horny, skinny pill”²¹¹ as material to a reasonable physician’s prescribing decision, because no reasonable physician would interpret a vague slogan as a scientific

²⁰⁶ See Kesselheim, Mello, and Studdert, *Strategies and Practices in Off-Label Marketing of Pharmaceuticals* at *4–5 (cited in note 174).

²⁰⁷ See *Simeon Management Corp v Federal Trade Commission*, 579 F2d 1137, 1145 (9th Cir 1978).

²⁰⁸ See FDA Guidance on Scientific Exchange at *2–3 (cited in note 58).

²⁰⁹ Note that this is true even if the audience member were to make a decision consistent with the marketing goal: though the claim might prompt the audience to investigate the data supporting that decision, reasonable audience members would make a prescribing decision only if the results of the investigation supported it. Thus, the claim itself would add negligible support compared to what already exists in the market. For this reason, courts applying the FTC Act have been hesitant to sanction companies for making general claims about product performance absent evidence that the advertiser intended to deceive consumers. See, for example, *In the Matter of Firestone Tire & Rubber Co*, 81 FTC 398, 460–62 (1972) (finding that naming a tire “Safety Champion” did not amount to misleading advertising under the FTC Act, because the name was too general to be understood as a safety claim). See also Vincent N. Palladino, *Lanham Act “False Advertising” Claims: What Is a Plaintiff to Do?*, 101 Trademark Rptr 1601, 1630 (2011) (suggesting that a trivial misrepresentation would not influence purchasing decisions).

²¹⁰ For an example from the FTC context, see *National Commission on Egg Nutrition v Federal Trade Commission*, 570 F2d 157, 163–64 (7th Cir 1977).

²¹¹ GSK Complaint at *19 (cited in note 1).

description of the drug's effects.²¹² On the other hand, a court would expect a reasonable physician to rely on the factual accuracy of the data and scientific conclusions presented in GlaxoSmithKline's seminars, marketing materials, and publications.

b) Medical considerations relevant to materiality. The materiality analysis would require courts to determine how a reasonable physician would evaluate whether the expected benefits of a medication outweigh the costs, taking into account the unique circumstances of specific cases.²¹³ In this context, the realities of medical practice are highly relevant to the materiality analysis. As a first step to analyzing a reasonable physician's reaction to an off-label claim, courts must identify the kinds of cases to which the physician might apply the information.²¹⁴ Physicians may encounter wide variation in risk-benefit preferences, even among patients with similar illnesses. For example, a patient with a poor prognosis or severe symptoms might be willing to tolerate a high risk of adverse side effects in order to try a new treatment.²¹⁵ Since a claim's materiality may differ among distinct patient populations, it is necessary for courts to assess materiality for both high-risk and low-risk scenarios.

For each scenario, courts would also need to consider how great a role the off-label claim plays in a reasonable physician's overall prescribing analysis, given the norms of medical practice.²¹⁶ As the FDCA's explicit endorsement of physicians' prescribing decisions²¹⁷ and common law's "learned intermediary"

²¹² The FTC has noted that a statement is not materially misleading if it is made under circumstances in which the target audience should understand the representation to be puffery. See *Clorox Co Puerto Rico v Proctor & Gamble Commercial Co*, 228 F3d 24, 38 (1st Cir 2000). "Puffery is an exaggeration or overstatement expressed in broad, vague, and commendatory language." *Castrol Inc v Pennzoil Co*, 987 F2d 939, 945 (3d Cir 1993).

²¹³ Importantly, courts have substantial experience with the "reasonable physician" standard, which is consistently invoked in medical malpractice cases. Jeffrey A. Van Detta, *Dialogue with a Neurosurgeon: Toward a Dépeçage Approach to Achieve Tort Reform and Preserve Corrective Justice in Medical Malpractice Cases*, 71 U Pitt L Rev 1, 68 n 150 (2009).

²¹⁴ See Palladino, 101 Trademark Rptr at 1626–31 (cited in note 209) (describing how consumer reliance is assessed).

²¹⁵ See Hutt, Merrill, and Grossman, *Food and Drug Law* at 729 (cited in note 15).

²¹⁶ False advertising cases generally consider advertising norms when assessing materiality. See, for example, *Everest Capital Ltd v Everest Funds Management, LLC*, 393 F3d 755, 763–64 (8th Cir 2005) (holding that an advertisement was not likely to be material to purchasing decisions in light of evidence showing that it did not tend to deceive the relevant consumer population).

²¹⁷ See Part II.B.2.

tradition suggest,²¹⁸ doctors are sophisticated decisionmakers who engage in a multipronged analysis when evaluating medical claims.²¹⁹ The rise of evidence-based medicine—the “conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients”²²⁰—in medical schools and medical practice over the past twenty years has made critical evaluation of scientific evidence a regular part of medical practice.²²¹

Numerous databases, clinical reference tools, and journals devoted specifically to meta-analysis of scientific evidence about medical treatments are available to help doctors independently evaluate drug-marketing claims.²²² Such resources develop content in response to prescribing habits and, as such, are likely to identify key off-label prescribing trends.²²³ The availability of these tools, combined with widespread concern about the veracity of drug-marketing claims that is described in both the medical²²⁴ and popular²²⁵ press, suggests that a reasonable physician would prescribe a drug based on an off-label claim only after consulting such tools as needed.

Consider, for example, a reasonable general practitioner who learned about off-label uses of Wellbutrin through a GlaxoSmithKline sales call or seminar.²²⁶ In assessing the off-label information’s materiality, a court would first consider the types of cases in which the general practitioner might have occasion to use the information.²²⁷ If most prescribing physicians are simply deciding whether to prescribe Wellbutrin or an otherwise

²¹⁸ See text accompanying note 194.

²¹⁹ See *Comments on Submissions concerning First Amendment Issues FDA Docket No. 02N-0209* *5 n 6 (Washington Legal Foundation, Oct 28, 2002), archived at <http://perma.cc/XQ3G-NLK2>. See also generally Evidence-Based Medicine Working Group, *Evidence-Based Medicine: A New Approach to Teaching the Practice of Medicine*, 268 JAMA 2420 (1992).

²²⁰ David L. Sackett, et al, *Evidence Based Medicine: What It Is and What It Isn't*, 312 Brit Med J 71, 71 (1996).

²²¹ See *Evidence-Based Medicine (EBM) Resources* (Dartmouth Biomedical Libraries), archived at <http://perma.cc/DH9H-MY43>.

²²² See id.

²²³ See id.

²²⁴ See Howard Brody, *The Company We Keep: Why Physicians Should Refuse to See Pharmaceutical Representatives*, 3 Annals Fam Med 82, 83 (2005).

²²⁵ See, for example, Daniel Carlat, *Dr. Drug Rep*, NY Times Magazine 64 (Nov 25, 2007) (detailing the author’s experience as a paid drug representative in order to call into question the neutrality and reliability of information distributed through drug companies’ promotional campaigns).

²²⁶ See text accompanying notes 198–99.

²²⁷ See Palladino, 101 Trademark Rptr at 1629–30 (cited in note 209).

equally suitable alternative, receiving information about GlaxoSmithKline's small-scale Wellbutrin studies might lead a doctor to prescribe Wellbutrin rather than the alternative.²²⁸ For example, a doctor assessing a new patient with mild depression stemming from a gambling addiction might, on the margin, elect to prescribe Wellbutrin rather than the alternative antidepressant Prozac. In such a case, the court would find that GlaxoSmithKline's claims had a material effect on the doctor's decisions.

If the typical case were more complex, however, the court's analysis would also involve a deeper investigation of the off-label claims' actual impact on physicians' prescribing decisions. Given the reasonable general practitioner's aversion to high-risk and innovative treatments, most physicians would seek additional information before prescribing Wellbutrin for a new use. If that is the case, the court would also assess how much weight the physician would give to GlaxoSmithKline's off-label claims in light of the other informational sources that the reasonable physician would consider.²²⁹ For example, before suggesting that patients switch to Wellbutrin from an alternative drug, the physician might peruse the professional literature for more information about her peers' experiences with Wellbutrin. If the literature provided ample support for the decision to switch the patient's medication—such as independent studies substantiating Wellbutrin's off-label claims, indications that the risks of switching to Wellbutrin were low, or strong anecdotal evidence from respected experts—the court could conclude that GlaxoSmithKline's off-label claims did nothing more than prompt physicians to check the literature. In that case, the court would find the off-label claims immaterial.

3. Step three: identifying misrepresentation.

If a court applying the false advertising statutes finds that a reasonable member of the target audience for the advertisement would take material action based on an allegedly misleading

²²⁸ For an example of such an analysis, see *Osmose, Inc v Viance, LLC*, 612 F3d 1298, 1319 (11th Cir 2010) (“In order to establish materiality, the plaintiff must demonstrate that ‘the defendant’s deception is likely to influence the purchasing decision.’”).

²²⁹ For an example of such an analysis, see *Suntree Technologies, Inc v Ecosense International, Inc*, 693 F3d 1338, 1349 (11th Cir 2012) (dismissing a false advertising claim partly because members of the intended audience did not make decisions based on the advertising).

advertisement, then the court next determines whether the advertising claim indeed misrepresents the facts.²³⁰ To resolve whether a claim misrepresents the facts, courts must first determine what the facts are and then decide whether the advertising claim accurately represents them. This is particularly challenging in cases involving the interpretation of scientific data, which are probabilistic.²³¹ Courts address this issue by assessing whether scientific data are true and provide a “reasonable basis” for an advertising claim.²³²

To reach this reasonable-basis finding under the false advertising statutes, a court determining whether an advertisement is misleading must first examine the factual basis for the claim. In the context of off-label marketing, scientific tests provide the relevant factual basis. To avoid a finding of misrepresentation, an advertiser must demonstrate that *reliable* scientific tests produced the data that support the claim.²³³ Courts determine the reliability of scientific tests by considering whether the pertinent study was conducted using a scientifically acceptable methodology,²³⁴ by qualified experts,²³⁵ and in a manner that reflects the actual conditions of consumer use.²³⁶ If the underlying scientific tests are reliable, courts then ask whether the data are adequate to support the claim.²³⁷ To do so, courts consider whether the advertising claim accurately characterizes the

²³⁰ See *FTC Policy Statement on Deception* (cited in note 121). A claim can misrepresent facts by stating a claim that the advertiser knows to be either unsupported by research or affirmatively false. See *Federal Trade Commission v National Urological Group, Inc*, 645 F Supp 2d 1167, 1190 (ND Ga 2008).

²³¹ See Peter W. Huber, *Galileo’s Revenge: Junk Science in the Courtroom* 214 (Basic Books 1993) (“Science does search for absolute and immutable truths. The search does progress. But it does not end.”).

²³² *Federal Trade Commission v Pharmtech Research, Inc*, 576 F Supp 294, 302 (DDC 1983). Courts consider whether the claim was substantiated at the time that it was made. See FTC, *FTC Policy Statement regarding Advertising Substantiation* (cited in note 170) (“[A]dvertisers will not be allowed to create entirely new substantiation simply because their prior substantiation was inadequate.”).

²³³ See *SmithKline Beecham Consumer Healthcare, LP v Johnson & Johnson—Merck Consumer Pharmaceuticals Co*, 906 F Supp 178, 182 (SDNY 1995).

²³⁴ See David Bernstein and Bruce Keller, *The Law of Advertising, Marketing and Promotions* § 3.03(2) & n 20 (Law Journal 2014), citing *In re Ciba Vision Corp (DAILIES AquaComfort Plus)*, NAD Case No 5107 (Nov 17, 2009).

²³⁵ See Bernstein and Keller, *The Law of Advertising* at § 3.03(2) & n 21 (cited in note 234), citing *In re Dell Computer Corp*, NAD Case No 4152 (Mar 2, 2004).

²³⁶ See *S.C. Johnson & Son, Inc v Clorox Co*, 930 F Supp 753, 781–82 (EDNY 1996).

²³⁷ See Bernstein and Keller, *The Law of Advertising* at § 3.02(2) & n 20 (cited in note 234), citing *In re Bayer HealthCare, LLC*, NAD Case No 5330 (May 9, 2011).

magnitude of the effect observed²³⁸ and the statistical significance of the results.²³⁹

Sometimes an advertiser might state all this information explicitly.²⁴⁰ If an advertisement provides a complete description of the study methodology and results, the claim is necessarily an accurate representation of the facts.²⁴¹ But when an advertiser makes a claim without providing details about all these elements, the court must determine whether the study's design and claimed results converge to form a valid advertising claim, or whether the claim misrepresents the facts.

The courts' false advertising jurisprudence recognizes both explicit and implicit deceptiveness as forms of misrepresentation.²⁴² These two forms of misrepresentation approximately map onto "false" and "misleading" advertising. Explicitly deceptive statements correspond to "false" off-label statements. An explicitly "false" off-label statement might involve the misstatement of a drug's approval status or data from scientific studies.²⁴³

Conversely, implicitly deceptive advertising claims correspond to "misleading" off-label statements. Implicitly "misleading" claims are true as a matter of fact but nevertheless convey untrue meaning.²⁴⁴ Federal false advertising jurisprudence highlights two types of implicitly deceptive statements. First, a literally true claim could be misleading if it causes a reasonable member of the target audience to infer something other than the truth.²⁴⁵ Second, a claim could also be misleading if it omits information that is needed to qualify or contextualize the statement.²⁴⁶ This Section discusses each form of misrepresentation in turn.

²³⁸ See *Proctor & Gamble Co v Chesebrough-Pond's Inc*, 747 F2d 114, 119 (2d Cir 1984).

²³⁹ See *In the Matter of Bristol-Myers Co*, 102 FTC 21, 336 (1983), affd 738 F2d 554 (2d Cir 1984).

²⁴⁰ See *McNeil-PPC*, 351 F Supp 2d at 250–51 (finding that, when an advertising claim makes a specific statement about the level of support for its claim, the plaintiff "need only prove that the [studies] referred to . . . were not sufficiently reliable to permit one to conclude with reasonable certainty that they established the proposition for which they were cited") (quotation marks omitted).

²⁴¹ See *id.*

²⁴² See, for example, *National Urological Group*, 645 F Supp 2d at 1190.

²⁴³ See *Pharmtech Research*, 576 F Supp at 302.

²⁴⁴ See *Donaldson v Read Magazine, Inc*, 333 US 178, 188 (1948).

²⁴⁵ See *American Home Products*, 695 F2d at 696–97.

²⁴⁶ See *Alberty v Federal Trade Commission*, 182 F2d 36, 44 (DC Cir 1950).

a) *Literally true, but nevertheless misleading, claims.* A claim that is literally true may nevertheless be misleading if it is ambiguous or otherwise misrepresents product performance.²⁴⁷ In the false advertising context, courts determine whether a claim is misleading in this way by evaluating whether the level of scientific support for the claim is appropriate given the claim’s specificity.²⁴⁸ The more expansive the claim, the more scientific support is needed to justify it.²⁴⁹ The type, accessibility, and adequacy of the scientific evidence supporting the claim are also relevant.²⁵⁰ If the target audience for the advertisement can easily access and understand the underlying study data, a court is unlikely to find that the advertiser’s description misrepresents the data.²⁵¹

This analysis translates well to the off-label context because courts already assess whether drug advertisements pertaining to on-label uses are false or misleading.²⁵² The FDCA regulations on advertising claims require that the advertisement *as a whole* be a “true statement” about drug effectiveness.²⁵³ As a baseline, a nonmisleading statement about effectiveness must include a specific description of both the health effects claimed²⁵⁴ and the patient population to which the claim applies.²⁵⁵ If an advertisement meets these requirements, courts then examine whether the advertisement is consistent with the overall weight of

²⁴⁷ See *American Home Products*, 695 F2d at 697.

²⁴⁸ See *id.* at 696–97.

²⁴⁹ See *id.*

²⁵⁰ See *id.*

²⁵¹ See *American Home Products*, 695 F2d at 696–97.

²⁵² See, for example, *id.* at 685–86; *Bristol-Myers Co v Federal Trade Commission*, 738 F2d 554, 562–63 (2d Cir 1984); *Healthpoint, Ltd v Stratus Pharmaceuticals, Inc*, 273 F Supp 2d 769, 792–93 (WD Tex 2001).

²⁵³ 21 CFR § 202.1(e)(3)(i).

²⁵⁴ See 21 CFR § 202.1(e)(3)(ii):

The information relating to effectiveness shall include specific indications for use of the drug for purposes claimed in the advertisement; for example, when an advertisement contains a broad claim that a drug is an antibacterial agent, the advertisement shall name a type or types of infections and microorganisms for which the drug is effective clinically as specifically as required, approved, or permitted in the drug package labeling.

²⁵⁵ See 21 CFR § 202.1(e)(6)(i) (stating that an advertisement is misleading if it “[c]ontains a representation or suggestion . . . that a drug is . . . effective [] in a broader range of conditions or patients . . . than has been demonstrated by substantial evidence or substantial clinical experience”).

experimental or clinical evidence of the drug's safety and effectiveness.²⁵⁶

Though off-label claims may be based on a broader range of study designs than on-label claims supported by FDA clinical trials, the on-label advertising regulations provide useful guidance for assessing the weight of experimental evidence.²⁵⁷ For example, the regulations require that a drug-advertising claim reflects the realities of the study's design and the data collected.²⁵⁸ A drugmaker must ensure that a claim notes study limitations and deviations from clinical trial best practices or else accounts for these factors by reporting the study's margin of error.²⁵⁹ If a drugmaker chooses to include graphs and tables in its promotional materials, these graphics must provide an accurate visual representation of the "relationships, trends, [and] differences . . . among the variables or products studied."²⁶⁰ Finally, statements about results must provide a sound description of the statistical and clinical significance of the results, as well as the variability of the underlying data.²⁶¹

Returning to the Wellbutrin example, a court's first step in applying these factors would be to ascertain what GlaxoSmithKline actually claimed.²⁶² The government's complaint alleges, for example, that the firm promoted Wellbutrin as an effective "add-on" treatment for conditions that frequently accompany depression.²⁶³ To determine whether the underlying data supported a broad effectiveness claim, the court would need to next address whether the studies provided adequate and controlled measurements of improvements in these comorbid disorders, and whether the study results were statistically significant.²⁶⁴ If, on

²⁵⁶ See 21 CFR § 202.1(e)(6).

²⁵⁷ The FDA's application of these regulations is evident from the "Warning Letters" and "Notice of Violation Letters" that the agency sends to pharmaceutical companies. The agency maintains a public database of letters related to prescription drug promotion. See *Warning Letters and Notice of Violation Letters to Pharmaceutical Companies* (US Food and Drug Administration, Feb 5, 2015), archived at <http://perma.cc/RZK5-5VNP>.

²⁵⁸ 21 CFR § 202.1(e)(7).

²⁵⁹ 21 CFR § 202.1(e)(7)(i)–(iii).

²⁶⁰ 21 CFR § 202.1(e)(7)(iv).

²⁶¹ 21 CFR § 202.1(e)(7)(ii)–(v).

²⁶² See, for example, *American Home Products*, 695 F2d at 690 (beginning a discussion of allegations that the defendant's advertisements were misleading with a thorough analysis of what the advertisements in fact claimed).

²⁶³ GSK Complaint at *26 (cited in note 1).

²⁶⁴ See, for example, *American Home Products*, 695 F2d at 692 (assessing whether the results underlying the defendant's claims were statistically significant).

the other hand, GlaxoSmithKline were to state that the studies merely suggested that Wellbutrin could be effective for accompanying medical conditions—as opposed to making a broad effectiveness claim—the court would focus its analysis on whether the claims provided an accurate representation of the underlying data. For example, if GlaxoSmithKline’s promotional materials included graphs or statistics, the court would consider whether the firm presented the data in a consistent fashion that accurately portrayed the strength of each individual claim.

b) Misleading omissions. An advertisement that does not affirmatively assert a misleading claim may still mislead a reasonable consumer if it omits critical information. Typically, an omission is deceptive because, without it, the advertising claim is a half-truth: literally true, but lacking additional information that is needed to qualify or contextualize the rest of the claim.²⁶⁵ The FTC and courts have taken the position that, in the context of the FTC Act, an advertiser must provide all the information that a consumer could reasonably be expected to need to evaluate the advertising claim.²⁶⁶

Courts distinguish between half-truths and situations in which consumers infer something from an advertisement that is not justified by its content. For example, in *Alberty v Federal Trade Commission*,²⁶⁷ a drug company advertised an iron supplement as a remedy for weakness and tiredness.²⁶⁸ However, the supplement was effective only for patients with iron-deficiency anemia.²⁶⁹ The court held that the advertisement was a half-truth, because the drug company did not disclose that the supplement would have an effect on only those patients suffering from iron deficiency.²⁷⁰ The *Alberty* court also held, however, that a statement is not necessarily misleading simply because it does not contextualize a product’s shortcomings.²⁷¹ Thus, the drug company in that case was not required to state in its advertisement that only a small proportion of people who experience

²⁶⁵ See *Porter & Dietsch, Inc v Federal Trade Commission*, 605 F2d 294, 306 (7th Cir 1979).

²⁶⁶ See, for example, *Southwest Sunsites, Inc v Federal Trade Commission*, 785 F2d 1431, 1438 (9th Cir 1986).

²⁶⁷ 182 F2d 36 (DC Cir 1950).

²⁶⁸ *Id* at 37.

²⁶⁹ *Id*.

²⁷⁰ *Id* at 39.

²⁷¹ *Alberty*, 182 F2d at 39.

weakness and tiredness have iron-deficiency anemia.²⁷² While an advertiser must not omit information that makes the advertisement effectively false, it is not required to include all information that could affirmatively help consumers understand the product.²⁷³

The FTC's approach to omissions translates well to the FDCA off-label-marketing context. If, as in *Alberty*, an off-label statement excludes information that is necessary to adequately characterize the patient population and the use to which the claim applies, then the underlying scientific evidence cannot support the claim. For example, GlaxoSmithKline's claims about Wellbutrin would have been false or misleading if they did not clarify the metrics by which effectiveness was measured or if they failed to note that an exclusively adult-patient population was tested. Similarly, a statement about an off-label use would be misleading if it failed to note pertinent limitations of the study design or if it selectively presented information about the nature of the clinical study or data analysis that would lead a physician to draw incorrect conclusions about the product's effectiveness.²⁷⁴ A court would likely find that GlaxoSmithKline's statements were misleading if the company did not mention the Wellbutrin studies' small sizes and short durations.²⁷⁵ Similarly, if the firm failed to incorporate the results of its follow-up studies into its claims, a court might find that the firm's selective presentation of data constituted a misleading claim.²⁷⁶

²⁷² See *id.*

²⁷³ *Id.*

²⁷⁴ See, for example, *United States v Ninety-Five Barrels*, 265 US 438, 443–44 (1924) (determining that a manufacturer had made a misleading statement in violation of the FDCA by misrepresenting the process by which its vinegar was produced).

²⁷⁵ See 21 CFR § 202.1(e)(6)(v), (xiv)–(xv) (providing that an advertisement is misleading if it mischaracterizes the scope of the studies supporting the advertiser's claims). See also GSK Complaint at *20–21 (cited in note 1) (“GSK hired the Cooney/Waters Group [], a public relations firm, to promote and publicize a GSK-funded pilot study . . . [a]lthough the pilot study included only 25 patients who were on the drug for only eight weeks.”).

²⁷⁶ See 21 CFR § 202.1(e)(6)(iii)–(iv) (providing that an advertisement is misleading if it offers a selective presentation of data to support its claims).

CONCLUSION

In the late 1990s, the drug company Warner-Lambert hatched a plan to increase sales of Neurontin, an antiepileptic.²⁷⁷ Unlike GlaxoSmithKline’s marketing of Wellbutrin, Warner-Lambert’s efforts were an obvious investment in deception. The company promoted the drug—which its sales team dubbed “snake oil”—for bipolar disorder and neuropathic pain caused by disorders like Parkinson’s disease.²⁷⁸ Because the data on Neurontin’s effectiveness were ambiguous, Warner-Lambert engaged in an elaborate (and successful) scheme to publish positive results and suppress negative ones.²⁷⁹

The Neurontin case highlights the key interest at stake in the regulation of off-label marketing: patient welfare. Any rule for evaluating off-label promotional speech must protect patients from nefarious or careless pharmaceutical-company behavior. For all its flexibility, the false advertising approach would not compromise on safety. Take Warner-Lambert’s actions as an example: the company misrepresented the experimental support in a way that caused diligent psychiatrists and geriatricians to prescribe an ineffective drug for seriously ill patients.²⁸⁰ It wouldn’t be a close case.

The false advertising framework advanced in this Comment makes a difference only in close cases—instances in which physicians are attempting to distinguish among equally promising treatment options. The US statutory scheme, common-law tradition, and Supreme Court jurisprudence all support the idea that more-accurate information helps physicians make better decisions. The fact-driven false advertising analysis promotes the dissemination of such useful information in a manner that also encourages drug companies to shoulder an efficient share of the burden in ensuring patient safety. Courts seeking a definition of “false or misleading” in light of *Caronia* and *POM Wonderful* would do well to adopt this approach.

²⁷⁷ See *In re Neurontin Marketing and Sales Practices Litigation*, 2011 WL 3852254, *2–6 (D Mass).

²⁷⁸ *In re Neurontin Marketing and Sales Practice Litigation*, 712 F3d 21, 26 (1st Cir 2013).

²⁷⁹ See *id.* at 27–28.

²⁸⁰ See *id.* at 30.