FOOD AND DRUG LAW JOURNAL

GEORGETOWN UNIVERSITY LAW CENTER

2017-2018

FOOD AND DRUG LAW JOURNAL

VOLUME 73 NUMBER 2 2018

210 Remarks by the Commissioner of Food and Drugs, Scott Gottlieb, MD
FDLI Annual Conference: May 3, 2018, Washington, DC

Manuscripts presented at the 4th Annual
Food and Drug Law Journal Symposium:

FDA and Health Behavior Regulation

October 20, 2017, Georgetown University Law Center

221 Implementing a Public Health Perspective in FDA Drug Regulation
Patricia J. Zettler, Margaret Foster Riley, and Aaron S. Kesselheim

257 Off-Label Communications: The Prodigal Returns
Jeffrey Chasnow and Geoffrey Levitt

276 Should FDA Try to Move Smokers to E-Cigarettes and Other Less Harmful Tobacco Products and, If So, How?
Eric N. Lindblom

319 "Natural" Food Claims: Industry Practices, Consumer Expectations, and Class Action Lawsuits
Neal Hooker, Christopher T. Simons, and Efthimios Parasidis

Student Note

338 Agribusiness and Antibiotics: A Market-Based Solution
Allison Parr

FDLI

GEORGETOWN LAW

O'NEILL INSTITUTE FOR NATIONAL & GLOBAL HEALTH LAW
GEORGETOWN LAW

Off-Label Communications: The Prodigal Returns

JEFFREY CHASNOW AND GEOFFREY LEVITT*

INTRODUCTION

Recent changes in law and policies relating to "off-label" product communications by manufacturers (OLPC) bring to mind the biblical parable of the Prodigal Son.[1] In the parable, the Prodigal Son behaves very badly but—to the dismay of his dutiful brother—is welcomed back by their forgiving father. Like the Prodigal, OLPC has a checkered history; for many years, OLPC was banished and distrusted. With a boost from the First Amendment, however, OLPC is rejoining the communities of medical practice and discussion. Much as the wise father welcomed his Prodigal Son home, FDA similarly needs to reconsider its traditions and biases against OLPC.

As in the parable, not everyone welcomes OLPC's return. Opponents of OLPC envision a "parade of horribles" that might result if manufacturers are given freer rein to discuss scientific data that FDA has not included in a product's label. They worry that looser restrictions on OLPC will result in an anarchic flood of confusing and even misleading information about FDA-approved products. Some contend that looser regulation of OLPC not only will disrupt FDA's control of information about products that the agency has cleared, but also will impair FDA's ability to prevent sales of "no-label" medical products—that is, new products or new uses of existing products that have not been subject to any FDA review or clearance.

These are valid concerns. As demonstrated in this Article, however, broad restrictions on OLPC for *all* medical products are not appropriate—constitutionally or as a policy matter—to protect against independent miscommunications about *some* products. Prescribers routinely rely on off-label information when treating patients, and federal law by design protects their freedom to do so. Because product manufacturers have deep knowledge of their products, they are obvious conduits for beneficial off-label information. FDA rules and enforcement policies, however, continue to prohibit most OLPC.

FDA's restrictive approach toward OLPC dates back to an earlier era that was very different, both legally and medically, from today. But FDA has been very slow to adapt its approach to modern constitutional norms and medical practice. As it has for over 50 years, the agency continues to treat both manufacturers and prescribers with presumptive distrust. This article provides legal analysis and real-world examples that demonstrate why it is important for FDA to modify its outdated

* Jeffrey Chasnow and Geoffrey Levitt serve as Chief Counsels at Pfizer, Inc and are, respectively, Chief Counsel at Pfizer Innovative Health and Chief Counsel for Regulatory, Environmental, and Global Supply.

[1] *Luke* 15:11–32.

policies and to adopt less-restrictive regulatory approaches that can, in many cases, improve patient care.

This Article proceeds as follows: Part I describes the legal context in the 1960s and 1970s, when FDA developed its restrictive approach to OLPC, and important changes in the legal landscape that have occurred more recently. Part II assesses the grounds that opponents of broader OLPC assert in defense of FDA's traditional, restrictive approach, and summarizes the benefits that broader OLPC may provide. As these sections make clear, the question FDA now faces is not how to defend its current OLPC policies, but how the agency should adapt its regulatory approach to modern conditions.

To inform this inquiry, Part III provides examples of beneficial OLPC that any new regulatory approach should aim to protect and enable, but that are inhibited under current regulation. Part IV offers suggestions for constructing a new regulatory regime.

I. LEGAL CONTEXT FOR FDA'S RESTRICTIONS ON OLPC: YESTERYEAR AND TODAY

The concept of OLPC is a byproduct of FDA's licensing authority, which was first bestowed upon the agency by the Food, Drug, and Cosmetic Act (FDCA) in 1938.[2] The FDCA required that FDA review and approve new medical products for safety before they could be sold in interstate commerce.[3] In 1962, the Kefauver-Harris Amendments to the FDCA added a requirement that drug sponsors demonstrate efficacy as well as safety as a condition for product approval.[4] As is often noted, both of these congressional actions were undertaken in response to public health threats associated with unapproved medicines.[5]

At the same time that Congress gave FDA a critical gatekeeping role for medical products, it also preserved the freedom of physicians to use approved products outside the terms of their licenses (that is, "off-label"). In approving and regulating medical products, therefore, FDA must achieve a "somewhat delicate balance" of "difficult (and often competing) objectives": setting the terms of product licenses while, at the same time, respecting prescribers' discretion to use products off-label.[6]

The policies FDA developed for OLPC generally prohibit manufacturers from engaging in OLPC except when and as FDA allows them to do so.[7] For the most part, this limits manufacturer communications to information that is contained in the

---

[2] Federal Food, Drug, and Cosmetic Act, Pub L. No. 75-717, 52 Stat. 1040, 102, 104 (1938) (codified as amended at 21 U.S.C. § 321 (2018)).

[3] As the result of subsequent amendments, the FDCA now contains similar but separate premarket approval processes for drugs, devices, and biologics. The principles discussed in this Article generally apply to all of them, so although the discussion focuses on drugs, it is relevant also to medical devices and biologics that require premarket FDA approval.

[4] Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified as amended at 21 U.S.C. § 321 (2018)).

[5] *See* Jeffrey Chasnow & Geoffrey Levitt, *Preemption of Non-Federal Restraints on Off-Label Product Communications*, 71 FOOD & DRUG L.J. 249, 251–53 (2016).

[6] Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 348–50 (2001).

[7] *See* United States v. Caronia, 703 F.3d 149, 152–55 (2d Cir. 2012)*; see generally,* Chasnow & Levitt, *supra* note 5, at 252–53.

FDA-approved product label. Information that is not in the label can be communicated only if it is consistent with the label and is based on "substantial evidence."[8]

In the early 1970s, FDA codified this approach in regulations that remain in force today,[9] and the agency has continued to restrict OLPC through regulatory guidance and enforcement actions. When FDA first established its policies, the agency did not factor in First Amendment principles. There appeared to be no cause to do so, because FDA viewed OLPC as "commercial speech"[10] and the Supreme Court did not explicitly recognize First Amendment protections for commercial speech until 1976.[11] For some years thereafter, the Court's emergent commercial speech doctrine seemed to afford only provisional protections for entities operating under government-issued licenses.[12]

Since at least 1996, however, the Court has steadily broadened First Amendment protections for commercial communications.[13] As a preeminent First Amendment scholar recently observed, "it is difficult to find a Supreme Court decision upholding governmental suppression of truthful commercial speech in the last 25 years."[14] Recent decisions indicate that commercial speech may enjoy the same levels of heightened scrutiny afforded to non-commercial communications.[15] With respect to OLPC, the Supreme Court's decision in *Sorrell v. IMS Health, Inc.*, in 2011, is particularly meaningful. *Sorrell* addressed the validity of a Vermont law that

---

[8] *See* FOOD & DRUG ADMIN., MEMORANDUM: PUBLIC HEALTH INTERESTS AND FIRST AMENDMENT CONSIDERATIONS RELATED TO MANUFACTURER COMMUNICATIONS REGARDING UNAPPROVED USES OF APPROVED OR CLEARED MEDICAL PRODUCTS 35–47 (2017) [hereinafter FDA 2017 MEMO ON OLPC].

[9] 21 C.F.R. § 202.1(e)(6) (2018) (originally enacted as Prescription Drug Advertisements, 40 Fed. Reg. 14,019 (Mar. 27, 1975)).

[10] There is a substantial question whether that characterization was correct. The Supreme Court has defined "commercial speech" as speech that does "'no more than propose a commercial transaction.'" Va. St. Bd. of Pharmacy v. Va. Citizens Consumer Council, 425 U.S. 748, 762 (1976) (quoting Pittsburgh Press Co. v. Human Rights Comm'n, 413 U.S. 378, 385 (1973)). As FDA itself has acknowledged, OLPC often consists of much more than a barebones sales pitch. *See* Chasnow & Levitt, *supra* note 5, at 254; *see also* Jennifer L. Herbst, *Off-Label "Promotion" May Not Be Merely Commercial Speech*, 88 TEMP. L. REV. 43, 74 (2015) ("Much of the information on off-label uses is part of the larger universe of scientific speech, which generally receives strict scrutiny protection like political speech.").

[11] Prior to 1976, the Supreme Court had summarily rejected suggestions that the First Amendment protected commercial speech. *E.g.*, Valentine v. Chrestensen, 316 U.S. 52, 54 (1942) ("[T]he Constitution imposes no . . . restraint on government as respects purely commercial advertising."). The Court explicitly reversed that approach in *Va. St. Bd. of Pharmacy. See* 425 U.S. at 758–70.

[12] *See* Posadas de P.R. Assocs. v. Tourism Co. of P.R., 478 U.S. 328, 345–46 (1986) ("[T]he greater power to completely ban casino gambling necessarily includes the lesser power to ban advertising of casino gambling."), *overruled by* 44 Liquormart, Inc. v. Rhode Island, 517 U.S. 484, 508–14 (1996).

[13] *See 44 Liquormart*, 517 U.S. at 512 ("[T]he First Amendment directs that government may not suppress speech as easily as it may suppress conduct, and that speech restrictions cannot be treated as simply another means that the government may use to achieve its ends. These basic First Amendment principles clearly apply to commercial speech . . . .").

[14] Martin H. Redish, *Commercial Speech and the Value of Free Expression*, CATO INST. POL'Y ANALYSIS NO. 813, 2 (2017), https://object.cato.org/sites/cato.org/files/pubs/pdf/pa_813.pdf [https://perma.cc/J47N-C7BH].

[15] *See* Sorrell v. IMS Health, Inc., 564 U.S. 522, 565–67 (2011) (holding that content-based restrictions on speech are subject to heightened scrutiny, even if the speech were considered to be commercial speech).

prohibited pharmaceutical manufacturers—but no other speakers—from using information about doctors' prescribing practices to inform marketing strategies. Noting that First Amendment protections have "great relevance in the fields of medicine and public health, where information can save lives," the Court invalidated the Vermont law's content- and speaker-based restrictions on manufacturer's promotional communications to physicians.[16]

The constitutionality of FDA's restrictions on OLPC was tested in a criminal case that was pending on appeal when *Sorrell* was decided. In *United States v. Caronia*, a pharmaceutical sales representative was convicted of a misbranding offense for promoting an approved product off-label. Reversing the conviction, the Second Circuit held that under *Sorrell* and other consistent case law, the FDCA should be construed "as not prohibiting and criminalizing the truthful off-label promotion of FDA approved prescription drugs."[17] *Sorrell* and *Caronia* have removed any doubt that FDA's regulatory approach is woefully out of date.[18]

In the wake of *Sorrell* and *Caronia,* and in response to requests from industry groups, FDA in 2014 announced that it would reconsider its policies relating to OLPC.[19] As of this writing in early 2018, however, the agency has made little—if any—progress in that endeavor. Although FDA invited public comments and discussion on how to reform its regulatory framework,[20] the regulatory approach of the 1960s−1970s remains in place. Guidance documents that FDA issued in January 2017,[21] purportedly with the goal of facilitating appropriate OLPC,[22] only reinforce

---

[16] *Id.* at 566, 571–80.

[17] United States v. Caronia, 703 F.3d 149, 168 (2d Cir. 2012).

[18] *See* Amarin Pharma, Inc. v. Food & Drug Admin., 119 F. Supp. 3d 196, 226–27 (S.D.N.Y. 2015) ("FDCA's drug-approval framework predates modern First Amendment law respecting commercial speech."). While our focus is on the constitutional invalidity of restrictions on OLPC, there is also a substantial question whether FDA has statutory authority to limit manufacturer communications to "substantial evidence." The FDCA states a "substantial evidence" standard only for product *approvals*, *e.g.,* 21 U.S.C. § 355(d)(5) (2018), and nowhere authorizes FDA to apply this standard to product *communications.* One commentator has argued that repeated references to "substantial evidence" in the FDCA's provisions regarding product approvals underscores the importance of this standard to product regulation and thus impliedly authorizes use of "substantial evidence" as a limitation on manufacturer communications. Nathan Cortez, *The Statutory Case Against Off-Label Promotion*, 83 U. CHI. L. REV. 124, 138–39 (2017). Significant flaws in this perspective include: (1) the FDCA's multiple and consistent iterations of "substantial evidence" as a standard *only* for product approvals actually supports the *negative* implication that Congress did not intend to apply the standard to manufacturer communications; (2) the suggested affirmative implication raises constitutional concerns that should be avoided, *see Caronia*, 703 F.3d at 160, 167–69; 3) the affirmative implication is in tension with FDA's statutory obligation "to regulate [medical products] without directly interfering with the practice of medicine." *Buckman*, 531 U.S. at 350.

[19] Letter from Leslie Kux, Assistant FDA Commissioner for Policy, to Alan R. Bennett, Joan McPhee, Paul Kalb, & Coleen Klasmeier, at 9, Nos. FDA-2011-P-0512 and FDA-2013-P-1079 (June 6, 2014).

[20] Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products, 81 Fed. Reg. 60299 (Food & Drug Admin. Sept. 1, 2016) (notice of public hearing and request for comments).

[21] FOOD & DRUG ADMIN., DRAFT GUIDANCE, MEDICAL PRODUCT COMMUNICATIONS THAT ARE CONSISTENT WITH THE FDA-REQUIRED LABELING—QUESTIONS AND ANSWERS (Jan. 2017) [hereinafter "CONSISTENT WITH LABEL" DRAFT GUIDANCE]; FOOD & DRUG ADMIN., DRAFT GUIDANCE, DRUG AND DEVICE MANUFACTURER COMMUNICATIONS WITH PAYORS, FORMULARY COMMITTEES, AND SIMILAR ENTITIES – QUESTIONS AND ANSWERS GUIDANCE FOR INDUSTRY AND REVIEW STAFF (Jan. 2017).

[22] FDA 2017 MEMO ON OLPC*, supra* note 8, at 20–21.

the traditional regime by providing examples of what FDA *might* allow, while reasserting FDA's claimed authority to disallow any OLPC of which it disapproves.[23]

II. PLUSSES AND MINUSES OF BROADER OLPC

FDA's public docket, and a flood of commentary in law journals and other publications, outline the terms of debate among proponents and opponents of broader OLPC. In essence, proponents claim that broader OLPC will improve public health by providing prescribers greater access to information about new and emerging treatment options. Opponents, for their part, claim that broader OLPC is more likely to harm public health by exposing patients to treatments whose benefits are unproven and whose risks are unknown. Opponents bear the heavier burden, because the First Amendment favors the free flow of information and disallows governmental restrictions unless they advance a significant public interest and are no broader than necessary to advance that interest;[24] without such a demonstration, the legitimacy of the asserted governmental interest in restricting OLPC dwindles to the vanishing point.

This portion of the Article comments on the main objections to broader OLPC, followed by a discussion of its potential benefits.

A. Objections to Broader OLPC: A Critique

Primary objections to broader OLPC include[25]: (1) communications by pharmaceutical manufacturers are riddled with commercial bias and thus undeserving of First Amendment protection; (2) restrictions on OLPC protect the public from misleading information; (3) restrictions on OLPC are necessary to motivate manufacturers to engage in medical research and to cooperate in FDA's premarket approval process. Opponents of broader OLPC also contend that (4) the First Amendment does not apply when the government uses speech to establish the

---

[23] *See, e.g.,* "CONSISTENT WITH LABEL" DRAFT GUIDANCE, *supra* note 21, at 9 (stating that, in addition to following the draft guidance, "firms should ensure their FDA-regulated promotional materials otherwise satisfy the applicable requirements of the FD&C Act and FDA's implementing regulations"); *see also* Washington Legal Foundation, Comments on Review of Existing Center for Drug Evaluation and Research Regulatory and Information Collect Requirements, at 3, No. FDA-2017-N-5101 (Dec. 7, 2017) ("a regulated entity ignores a 'non-binding' guidance (whether final or in draft form) at its peril, even when compliance is extremely expensive and the entity strongly believes that the guidance misstates statutory or constitutional law"), http://www.wlf.org/upload/litigation/misc/FDAComments-Useof GuidanceDocs.pdf [http:// perma.cc/4854-2KMU].

[24] *See* Sorrell v. IMS Health, Inc., 564 U.S. 522, 571–72 (2011) ("[T]he outcome here is the same whether a special commercial speech inquiry or a stricter form of judicial scrutiny is applied . . . . [T]he State must show at least that the statute directly advances a substantial governmental interest and that the measure is drawn to achieve that interest."); Thompson v. W. States Med. Ctr, 535 U.S. 357, 371 (2002) ("[I]f the Government could achieve its interests in a manner that does not restrict speech, or that restricts less speech, the Government must do so.").

[25] The objections addressed below are drawn from the FDA *2017 Memo on OLPC*, which reflects views submitted to FDA's docket as well as other published perspectives. It should be noted that despite its stated intent to "provide additional background and seek input" on issues relating to OLPC, FDA 2017 MEMO ON OLPC, *supra* note 8, at 1, the memorandum has an obvious oppositional slant. Moreover, considering the timing of the memorandum's issuance—two days before the inauguration of a new President—it is not clear if the memorandum reflects FDA's current thinking. Nonetheless, it is a useful compendium of oppositional thinking.

"intended use" element of a misbranding offense. As discussed below, none of these considerations justifies broad restraints on OLPC, as a constitutional or policy matter.

1. Manufacturer Communications Should Not Be Presumed to Be Distorted by Bias

The contention that restrictions on OLPC are justified to protect against manufacturer bias[26] runs squarely against *Sorrell*, which held that restrictions on speech by manufacturers are subject to heightened constitutional scrutiny, notwithstanding manufacturers' commercial interests.[27] Moreover, the contention that manufacturers—who have extensive information about their products[28]—need to be excluded from public discussions of product data rests on the plainly erroneous premise that, among healthcare stakeholders, only manufacturers have biases. This presumption of bias is itself a *governmental* bias that has no sanction under the First Amendment.[29]

At present the ability of any source, other than manufacturers themselves, to engage in OLPC is unrestricted, and the quality and accessibility of such sources is highly variable. Yet all stakeholders in the healthcare system, from payors to hospitals to government agencies to academic medical centers, have institutional interests that can potentially lead to conscious or unconscious bias. Why should every such stakeholder have a free pass to engage in OLPC (or in any communications related to medical products, for that matter), with the sole exception of manufacturers?

2. Banning <u>All</u> OLPC Is Not a Permissible Way to Prevent <u>Some</u> OLPC From Being Misleading

Opponents of broader OLPC cite the danger of inadequately substantiated medical product information coming into the marketplace prematurely, bringing with it the potential for ineffective treatment, poorly understood safety risks, and waste of healthcare resources. FDA itself has noted several examples of situations where relatively widespread off-label use has potentially led to adverse health

---

[26] *See* FDA 2017 MEMO ON OLPC, *supra* note 8, at 9–10 (contending that FDA control of medical information is necessary to correct biases inherent in nongovernmental data presentations).

[27] *See Sorrell*, 564 U.S. at 566–67; *see also* Reed v. Town of Gilbert, 135 S. Ct. 2218, 2229 (2015) ("[T]he First Amendment expressly targets the operation of the laws . . . rather than merely the motives of those who enacted them . . . . '[I]t is no answer . . . to say . . . that the purpose of these regulations was merely to insure high professional standards and not to curtail free expression.'") (quoting NAACP v. Button, 371 U.S. 415, 438–39 (1963)).

[28] *See* United States v. Caputo, 517 F.3d 935, 939 (7th Cir. 2008) (given that off-label use "is lawful . . . doesn't it make a good deal of sense to allow speech by the device's manufacturer, which after all will have the best information?").

[29] *See* Ony, Inc. v. Cornerstone Therapeutics, Inc., 720 F.3d 490, 497–98 (2d Cir. 2013) (rejecting false advertising claims grounded on generalized assertion of bias); *see also* Jane R. Bambauer & Derek E. Bambauer, *Information Libertarianism*, 105 CAL L. REV. 335, 352 (2017) ("[T]here is no principled reason to treat profit-motivated speech as more dangerous than other forms of self-interested speech designed to gain influence, get hired, get elected, or get someone into bed."); Redish, *supra* note 14, at 11 ("There exists no rational basis on which to categorically set commercial speakers apart [from other speakers], other than the ideologically driven desire to penalize those who benefit from the capitalistic system. Such justification is pathologically inconsistent with the very foundations of the First Amendment the argument purports to implement.").

consequences, including the use of erythropoietin-stimulating agents to treat anemia associated with cancer, the use of estrogens to treat coronary artery disease, and the use of certain anti-arrhythmic drugs to treat asymptomatic ventricular arrhythmias.[30] No one would argue that off-label use of medical products is risk-free. But—as will be outlined below—some off-label uses provide significant potential benefits. It is far from clear that FDA's ban on *all* OLPC is necessary to mitigate the risks that only *some* OLPC may present.[31] A more balanced and constitutionally sound approach is to lift categorical restrictions on OLPC and implement appropriate quality standards.

3. Restrictions on OLPC Are Not Necessary to Maintain Incentives for Research and Premarket Review

Opponents of broader OLPC often argue that allowing manufacturer speech about unapproved uses will reduce or remove incentives for manufacturers to utilize the FDA approval process.[32] Maintaining the integrity of the FDA approval system is unquestionably important, and it is entirely possible that, in some instances, a manufacturer might conclude it is not worthwhile to seek approval for a particular use. Even with the ability to engage in broader OLPC, however, manufacturers will still have strong incentives to seek FDA approval for new indications. First and foremost, FDA approval will remain the gold standard for assessing a product's safety and efficacy for a particular use. Having FDA-approved efficacy claims, dosing information, and safety labeling will provide a manufacturer not only with the best defenses against legal challenges—e.g., product liability actions, *qui tam* claims under the False Claims Act, shareholder derivative lawsuits—but also with the strongest possible marketing position, especially against competing products that lack such approval. Such approval will also substantially improve opportunities for reimbursement of the approved use from both public and private insurers. Reputable manufacturers will also continue to value the scientific and clinical credibility that comes with agency approval. In this light, theoretical concerns about the potential that the product approval system may be undermined are insufficient to trump the First Amendment and public health imperatives at stake here.

4. Restrictions on OLPC Are Not Immune from First Amendment Protections

In addition to asserting the above justifications for FDA's restrictions on OLPC, opponents of broader OLPC also offer a rather paradoxical excuse: that FDA's restrictions don't actually impede speech but merely use OLPC as evidence of off-label intent.[33] To support this odd contention, the opponents rely principally on the following statement from a 1993 Supreme Court decision, *Wisconsin v. Mitchell*:

---

[30] FDA 2017 MEMO ON OLPC, *supra* note 8, at 48–52.

[31] *See* Thompson v. W. States Med. Ctr, 535 U.S. 357, 374 (2002) (rejecting government's assertion that ban on advertising of compounded drugs was needed to protect public health, noting this contention rested on the "questionable assumption that doctors would prescribe unnecessary medications").

[32] FDA 2017 MEMO ON OLPC, *supra* note 8, at 14–16.

[33] As FDA enforces the FDCA, "an approved prescription drug that is intended for an unapproved use would be misbranded because the drug does not meet the regulatory exemptions from the requirement that its labeling bear 'adequate directions for use.'" *Id.* at 37.

"The First Amendment . . . does not prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent."[34]

Neither the sentence quoted, nor the Court's decision in *Mitchell,* nor any other controlling precedent, fairly can be read to immunize evidentiary use of OLPC from First Amendment scrutiny. *Mitchell* addressed the constitutionality of a Wisconsin hate crimes law that provided a sentence enhancement for certain offenses committed with racial bias. Mitchell had committed an aggravated assault and received the sentence enhancement because statements he made showed that his attack was motivated by racial animus. The Court held that the First Amendment did not prohibit use of Mitchell's hateful speech to enhance his sentence.

Wisconsin's use of Mitchell's speech to enhance his sentence is worlds apart from the evidentiary use of OLPC to establish a misbranding offense. There was no question in *Mitchell* that the underlying offense, aggravated assault, had been committed: Mitchell and his accomplices beat a child so badly that the victim was in a coma for four days. Thus, application of a sentence enhancement under Wisconsin's hate crime law did not itself criminalize Mitchell's racially-biased speech, but merely used the speech to characterize his offense.[35] Had Mitchell not attacked the victim, but only yelled racial slurs at him, he would not have committed a crime under the Wisconsin hate crime law. The Court thus dismissed as "purely speculative" Mitchell's contention that evidentiary use of his racially-biased speech would chill free expression that is not connected with an underlying offense.[36]

By contrast, FDA's regulatory approach has a significant chilling effect on protected speech—as will be demonstrated by the examples set forth in the next part of this Article. When FDA uses a manufacturer's speech to prove intent, the impact on protected speech is not merely incidental[37] to establishing the offense of misbranding. The manufacturer's act of speaking, and the off-label content of the speech, are themselves what defines the manufacturer's sales activity as illegal. It is this direct impact on manufacturer speech that makes FDA's regulatory approach unconstitutional.[38]

---

[34] *Id.* at 21–22 (quoting Wisconsin v. Mitchell, 508 U.S. 476, 489 (1993)).

[35] *Mitchell*, 508 U.S. at 485–88.

[36] *Id*. at 488–89 ("The sort of chill envisioned [by Mitchell] is far more attenuated and unlikely than that contemplated in traditional 'overbreadth' cases."). The fallacy in reading *Mitchell* as a general detour around First Amendment protections is made plain by a simple example: consider a law that prohibits people from walking or congregating with the intent to criticize public officials. Under the flawed view of *Mitchell* that opponents of OLPC advocate, someone walking to a public protest would have no First Amendment protection against use of his/her criticisms as evidence of this offense. But the First Amendment plainly prohibits precisely this kind of regulation. *E.g.,* Edwards v. South Carolina, 372 U.S. 229, 237 (1963) (First Amendment protects "the peaceful expression of unpopular views").

[37] As the Supreme Court recently noted, a law affecting speech falls outside the First Amendment when its impact on speech is "only incidental to its primary effect on conduct." Expressions Hair Design v. Schneiderman*,* 137 S. Ct. 1144, 1150–51 (2017).

[38] A recent article seeks to cast doubt on the constitutional infirmity of FDA's restrictions on OLPC by referencing other laws that have intent elements. Christopher Robertson & Victoria Laurion, *Tip of the Iceberg II: How the Intended-Uses Principle Produces Medical Knowledge and Protects Liberty*, 11 N.Y.U. J.L. & LIBERTY 770, 789 (2017). The cited examples generally are inapt comparisons to the FDA regulatory scheme, however, because their impacts on protected speech are less significant and more closely-fit to appropriate regulation. *See* Jane R. Bambauer, *Snake Oil Speech*, 92 WASH. L. REV. 73, 106 (2017) ("*Caronia* has exposed the uncomfortable fact that much of the FDA's work is geared toward regulating information, not products.").

Is the outcome different when the OLPC is not the *only* evidence of misbranding—that is, when there is other evidence, in addition to the OLPC, suggesting that a manufacturer intends that its product be used off-label? Opponents of OLPC insist that it is, and that "*Caronia* left open the government's ability to prove misbranding on a theory that promotional speech provides evidence that a drug is intended for a use that is not included on the drug's FDA approved label."[39]

Although *Caronia* involved a restriction on OLPC that was based only on a manufacturer's speech, it does not follow that *Caronia*'s holding is wholly inapplicable to situations where non-speech evidence suggests a manufacturer's intent for a product to be used off-label. Numerous precedents make clear that the First Amendment protects against not only direct restrictions on speech, but also regulatory impacts that disadvantage selected speakers or content.[40] The Vermont law at issue in *Sorrell* was unconstitutional because of its discriminatory impact on pharmaceutical manufacturers.[41] The prospect that OLPC might be used in an enforcement action similarly disadvantages manufacturers and inhibits their speech.[42] The constitutional question is not whether speech is the *only* target of the government regulation, but whether the government's regulatory approach—even if aimed at behavior that is not protected speech—significantly inhibits protected speech. Because non-speech regulation of "intended use" often can chill protected speech, the Second Circuit, in *Caronia*, was correct in deciding that, under First Amendment principles, the FDCA should be construed "as not prohibiting and criminalizing the truthful off-label promotion of FDA approved prescription drugs."[43]

B. Benefits of Broader OLPC

The manufacturer of a medical product possesses an unparalleled level of information about that product, and is therefore in a position to offer the most complete and up-to-date picture of the product's safety and efficacy.[44] Under the rubric of "scientific exchange," FDA has long acknowledged that there is potential benefit to manufacturers' communicating off-label information and indeed that such communication is a necessary part of researching and developing new treatments. FDA has also long acknowledged that off-label use is a necessary part of medical practice and may even represent standard of care in certain situations.[45]

---

[39] *See* FDA 2017 MEMO ON OLPC, *supra* note 8, at 22 (quoting United States ex rel. Polansky v. Pfizer, Inc., 822 F.3d 613 n.2 (2d Cir. 2016)).

[40] *See, e.g.,* Reed v. Town of Gilbert, 135 S. Ct. 2218, 2230 (2015) ("[S]peech regulation targeted at specific subject matter is content based even if it does not discriminate among viewpoints within that subject matter.").

[41] Sorrell v. IMS Health, Inc., 564 U.S. 522, 563–66 (2011).

[42] *See* Amarin Pharma, Inc. v. Food & Drug Admin., 119 F. Supp. 3d 196, 221 (S.D.N.Y. 2015) (holding that history of enforcement against OLPC chills manufacturer speech).

[43] United States v. Caronia, 703 F.3d 149, 168 (2d Cir. 2012).

[44] Wyeth v. Levine, 555 U.S. 555, 578–79 (2009) ("Manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge.").

[45] FOOD & DRUG ADMIN., *Guidance, 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* (Jan. 2009).

It has also been widely acknowledged, including by FDA, that the randomized clinical trial results that form the basis of approved labeling are limited in their scope and in their relevance to real-world medical practice, such that the availability of other kinds of data and information, including real-world evidence, comparative analyses, and pharmacoeconomic information, can be of significant benefit to healthcare.[46]

III. NOT ALL OLPC IS THE SAME: THE NEED FOR MORE FLEXIBLE REGULATION

The prior discussion describes how FDA's traditional restrictions on OLPC rely on outdated legal principles that (1) have not evolved with First Amendment case law and (2) risk criminalizing and chilling truthful information that could benefit the medical community. Opponents of broader OLPC nonetheless insist that bright line rules limiting the content, speaker, context, and manner of OLPC are necessary not only to manage OLPC, but also to avoid a degradation of regulatory control that could lead to increased "no-label" sales of medical products.[47] As noted earlier, this fear is grossly overstated and turns the First Amendment on its head. Repeated precedents make clear that government regulators may not impose broad restrictions on speakers or content merely for reasons of administrative expediency or to avoid "slippery slope" effects.[48] FDA's public health mission is of course very important, but it does not bestow on the agency a regulatory easement across the First Amendment.

Instead of general restrictions, FDA should tailor its regulation to specific circumstances.[49] There is a wide spectrum of OLPC and contexts in which it may be used. Some kinds of off-label information for approved products might be similar to "no-label" product information—that is, unsubstantiated and overly suggestive of unproven product characteristics. But in many cases OLPC can help improve patient care, and the risks of overstatement can be managed with contextual information. A new regulatory regime should appropriately distinguish OLPC that is clearly beneficial and properly contextualized from its far-distant "no-label" cousin. Put another way: a manufacturer that communicates real-world data about a product that

---

[46] *See, e.g.,* 21st Century Cures Act, Pub. L. 114-255, § 3022 (2016) (codified as amended at 21 U.S.C. § 355g) (requiring FDA to evaluate the use of real-world evidence to help support approval of a new indication for an approved drug and to help satisfy post-approval requirements).

[47] *See* FDA 2017 MEMO ON OLPC, *supra* note 8, at 4–5.

[48] *See, e.g.,* Sorrell v. IMS Health, Inc., 564 U.S. 522, 577 (2011) (rejecting state's contention that "the force of speech can justify the government's attempts to stifle it"); *id.* at 578–79 ("The State may not burden the speech of others in order to tilt public debate in a preferred direction."); Thompson v. W. States Med. Ctr, 535 U.S. 357, 371 (2002) ("[I]f the Government could achieve its interests in a manner that does not restrict speech, or that restricts less speech, the Government must do so.").

[49] *Sorrell* and many other cases make clear that governmental regulation of speech, whether subject to intermediate or strict scrutiny, must be tailored to "ensure not only that the State's interests are proportional to the resulting burdens placed on speech but also that the law does not seek to suppress a disfavored message." 564 U.S. at 572. FDA's contention that its regulatory approach to OLPC is properly tailored because it restricts only manufacturer speech, FDA 2017 MEMO ON OLPC, *supra* note 8, at 25, is startlingly inconsistent with *Sorrell*, which invalidated a Vermont law precisely *because* its restrictions on information-sharing applied only to pharmaceutical manufacturers—" a narrow class of disfavored speakers." 564 U.S. at 573.

FDA has reviewed, approved, and closely monitored should not be subject to the same distrust and constraints as opportunists who operate wholly outside FDA's regulatory purview—e.g., selling whippets at a rock concert.[50]

The following are real-world examples of beneficial OLPC that, under FDA's traditional restrictions, would not be permissible. Pfizer was able to communicate this information in reliance on First Amendment principles. These examples provide some context for differentiating OLPC from "no-label" communications.

A. Dose Modifications

SUTENT® (sunitinib) is recognized in U.S. and European treatment guidelines as a standard-of-care for kidney cancer.[51] As with many oncolytics, patients taking SUTENT may experience uncomfortable side-effects or tolerability issues that can disrupt medication adherence and duration of therapy.[52] The FDA-approved label for SUTENT recommends a dose of 50 mg per day for four weeks, and then a two-week holiday from therapy (Schedule 4/2). The label also states that "dose interruption and/or dose adjustment in 12.5 mg increments or decrements is recommended based on individual safety and tolerability." The label does not recommend any specific schedule for dose interruption.[53]

Since 2013, multiple observational and retrospective studies have evaluated the merits of starting patients on Schedule 4/2, but modifying to a 2/1 schedule (two weeks of therapy/one week holiday) for patients who experienced tolerability issues.[54] These studies observed improved tolerability from the 2/1 regimen for patients who could not well tolerate the labeled 4/2 dosing regimen.[55] But FDA's regulations and enforcement policies—which limit manufacturer communications to information that is included in the product label and meets the standard of "substantial evidence"—prohibit manufacturer communications about the 2/1 dosing regimen.

FDA's January 2017 "consistent with label" draft guidance does not alleviate this problem. The draft guidance suggests that manufacturers might be able to communicate extra-label information that is consistent with FDA-required labeling. But the guidance has no binding legal effect and is expressly superseded by the "substantial evidence" standard in current regulations.[56] Moreover, the guidance specifically disapproves of manufacturer communications relating to a dosing regimen that "conflict" with the regimen recommended in the product label.[57] We would contend that the 2/1 regimen does not conflict with the approved labeling for

---

[50] *See* United States v. Travia, 180 F. Supp. 2d 115 (D.D.C. 2001).

[51] Sergio Bracarda, et. al., *How clinical practice is changing the rules: the sunitinib 2/1 schedule in metastatic renal cell carcinoma*, 17:3 EXPERT REV. OF ANTICANCER THERAPY 227, 227 (2017).

[52] *Id.*

[53] Current prescribing information for Sutent is available at *Drug Label Information*, DAILYMED (Nov. 28, 2017), https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=43a4d7f8-48ae-4a63-9108-2fa8e3ea9d9c [https://perma.cc/L3RN-8HW7].

[54] *See generally* Bracarda, *supra* note 51.

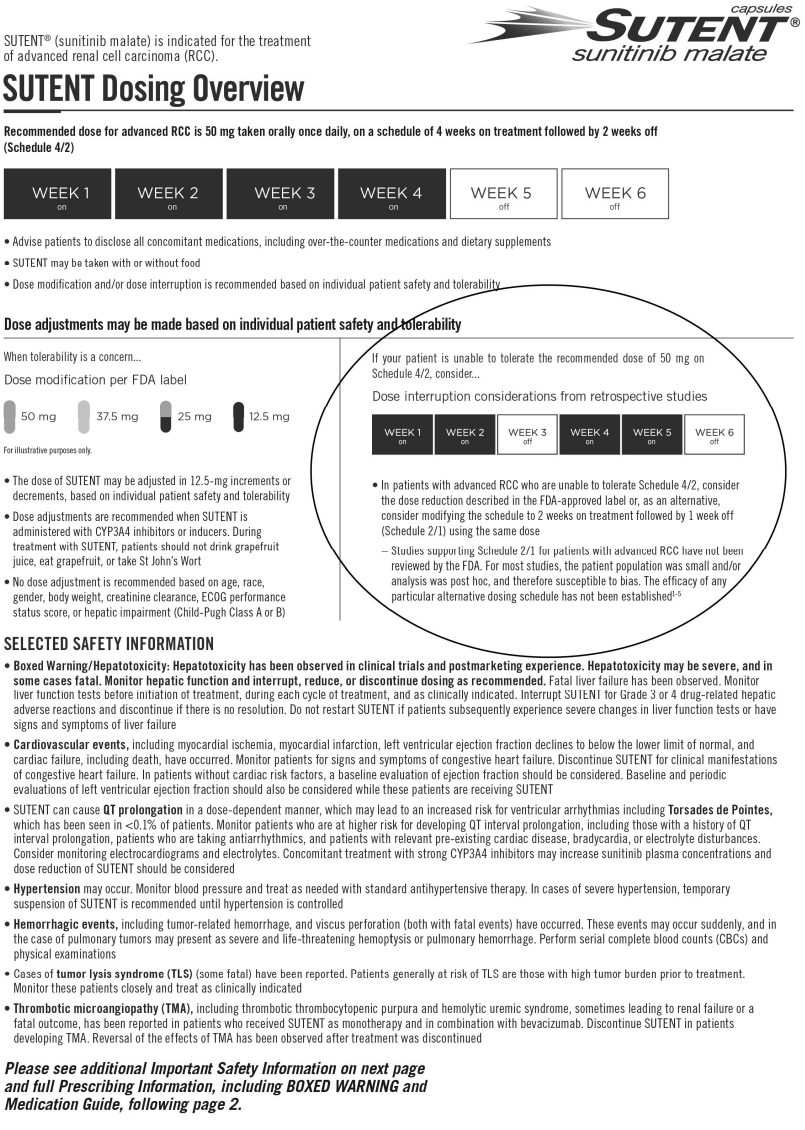
[55] *Id.* at 227–28, 231.

[56] "CONSISTENT WITH LABEL" DRAFT GUIDANCE, *supra* note 21, at 2 (noting that FDA guidance documents are not legally binding, but "describe the Agency's current thinking on a topic and should be viewed only as recommendations").

[57] *Id.* at 3–4.

SUTENT, which allows for dose-modification. But the guidance is not clear on this point (and, as noted, the guidance is superseded by FDA's "substantial evidence" regulation).

Pfizer ultimately was able to move forward with communications about this dosing regimen by applying First Amendment principles. As reflected in the accompanying excerpt from a Pfizer promotional visual aid, we do not "promote" the alternative dosing regimen, but simply share with prescribers that if a patient cannot tolerate the labeled dosing regimen, there are retrospective studies suggesting the alternative regimen. Our promotional materials make clear that these studies are not reflected in the product label and that for most of the studies, the patient populations were small and/or analysis was post hoc, and therefore susceptible to bias.



capsules SUTENT® sunitinib malate

SUTENT® (sunitinib malate) is indicated for the treatment of advanced renal cell carcinoma (RCC).

SUTENT Dosing Overview

Recommended dose for advanced RCC is 50 mg taken orally once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2)

WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5	WEEK 6
on	on	on	on	off	off

- Advise patients to disclose all concomitant medications, including over-the-counter medications and dietary supplements
- SUTENT may be taken with or without food
- Dose modification and/or dose interruption is recommended based on individual patient safety and tolerability

Dose adjustments may be made based on individual patient safety and tolerability

When tolerability is a concern...

Dose modification per FDA label

50 mg | 37.5 mg | 25 mg | 12.5 mg

For illustrative purposes only.

- The dose of SUTENT may be adjusted in 12.5-mg increments or decrements, based on individual patient safety and tolerability
- Dose adjustments are recommended when SUTENT is administered with CYP3A4 inhibitors or inducers. During treatment with SUTENT, patients should not drink grapefruit juice, eat grapefruit, or take St John's Wort
- No dose adjustment is recommended based on age, race, gender, body weight, creatinine clearance, ECOG performance status score, or hepatic impairment (Child-Pugh Class A or B)

If your patient is unable to tolerate the recommended dose of 50 mg on Schedule 4/2, consider...

Dose interruption considerations from retrospective studies

WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5	WEEK 6
on	on	off	on	on	off

- In patients with advanced RCC who are unable to tolerate Schedule 4/2, consider the dose reduction described in the FDA-approved label or, as an alternative, consider modifying the schedule to 2 weeks on treatment followed by 1 week off (Schedule 2/1) using the same dose
  - Studies supporting Schedule 2/1 for patients with advanced RCC have not been reviewed by the FDA. For most studies, the patient population was small and/or analysis was post hoc, and therefore susceptible to bias. The efficacy of any particular alternative dosing schedule has not been established[1-5]

SELECTED SAFETY INFORMATION

- **Boxed Warning/Hepatotoxicity: Hepatotoxicity has been observed in clinical trials and postmarketing experience. Hepatotoxicity may be severe, and in some cases fatal. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended.** Fatal liver failure has been observed. Monitor liver function tests before initiation of treatment, during each cycle of treatment, and as clinically indicated. Interrupt SUTENT for Grade 3 or 4 drug-related hepatic adverse reactions and discontinue if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have signs and symptoms of liver failure
- **Cardiovascular events,** including myocardial ischemia, myocardial infarction, left ventricular ejection fraction declines to below the lower limit of normal, and cardiac failure, including death, have occurred. Monitor patients for signs and symptoms of congestive heart failure. Discontinue SUTENT for clinical manifestations of congestive heart failure. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered. Baseline and periodic evaluations of left ventricular ejection fraction should also be considered while these patients are receiving SUTENT
- SUTENT can cause **QT prolongation** in a dose-dependent manner, which may lead to an increased risk for ventricular arrhythmias including **Torsades de Pointes,** which has been seen in <0.1% of patients. Monitor patients who are at higher risk for developing QT interval prolongation, including those with a history of QT interval prolongation, patients who are taking antiarrhythmics, and patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. Consider monitoring electrocardiograms and electrolytes. Concomitant treatment with strong CYP3A4 inhibitors may increase sunitinib plasma concentrations and dose reduction of SUTENT should be considered
- **Hypertension** may occur. Monitor blood pressure and treat as needed with standard antihypertensive therapy. In cases of severe hypertension, temporary suspension of SUTENT is recommended until hypertension is controlled
- **Hemorrhagic events,** including tumor-related hemorrhage, and viscus perforation (both with fatal events) have occurred. These events may occur suddenly, and in the case of pulmonary tumors may present as severe and life-threatening hemoptysis or pulmonary hemorrhage. Perform serial complete blood counts (CBCs) and physical examinations
- Cases of **tumor lysis syndrome (TLS)** (some fatal) have been reported. Patients generally at risk of TLS are those with high tumor burden prior to treatment. Monitor these patients closely and treat as clinically indicated
- **Thrombotic microangiopathy (TMA),** including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, sometimes leading to renal failure or a fatal outcome, has been reported in patients who received SUTENT as monotherapy and in combination with bevacizumab. Discontinue SUTENT in patients developing TMA. Reversal of the effects of TMA has been observed after treatment was discontinued

Please see additional Important Safety Information on next page and full Prescribing Information, including BOXED WARNING and Medication Guide, following page 2.

Many prescribers have told us that this information has been very helpful to their patients. A recent medical review article cited "the increasing use of the sunitinib 2/1 schedule [as] a good example of how oncologists modify the indicated dosing of oral anticancer drugs according to real-world clinical practice."[58]

B. Adverse Events

It is of course critical for prescribers and patients to understand the risks of potential adverse effects (AE) from drug treatment. The FDA-approved label includes detailed information on adverse events observed during pivotal trials, as well as events that are spontaneously reported as being associated with (but not necessarily caused by) use of commercial product. FDA generally does not include in the product label, however, results of meta-analyses of clinical trials or postmarket observational studies, as these analyses are not considered to be "substantial evidence." As a result, FDA's regulatory regime effectively prohibits manufacturers from communicating information from meta-analyses or observational studies (prospective as well as retrospective) that may have higher reliability than the essentially unfiltered AE information that FDA includes in the product label.

Pfizer's smoking cessation therapy, CHANTIX® (varenicline), presents a good example of why this can be problematic.[59] FDA approved CHANTIX in May 2006 as an aid to smoking cessation treatment for adults 18 and over. Within a year of approval, serious neuropsychiatric adverse events (NPS AEs), including AEs related to suicidality, began to be reported in postmarketing experience. As this signal emerged in 2007 to 2008, FDA added warnings and precautions to the CHANTIX labeling to alert prescribers and patients to the potential risk of such events. In July 2009, FDA added a boxed warning to the label to further highlight this safety information.

At that time, no large, population-based observational studies had analyzed the NPS safety of CHANTIX, and FDA did not consider the available clinical trial data adequate either to rule in or rule out an association between serious NPS AEs and the use of CHANTIX. In 2008, as a postmarketing requirement, FDA directed Pfizer and GlaxoSmithKline (GSK) to conduct a prospective, randomized and controlled trial to assess the risk of NPS AEs from CHANTIX, buproprion (GSK's product), and nicotine replacement therapy. Pfizer and GSK collaborated on a study known as EAGLES (Evaluating Adverse Events in a Global Smoking Cessation Study) to address FDA's postmarketing requirement.

By 2014, while EAGLES was still ongoing, several significant studies had explored the relationship between CHANTIX treatment and NPS AEs based on existing data. These included two meta-analyses of randomized, placebo-controlled trials conducted by Pfizer and four independent, large-scale, population-based observational studies comparing the NPS safety of CHANTIX to other smoking cessation agents. The two meta-analyses found no increase in the incidence of suicidal ideation and/or behavior and a similar incidence of common psychiatric

---

[58] Bracarda, *supra* note 51, at 231.

[59] The regulatory history of Chantix is recounted in a briefing document that FDA prepared in connection with an advisory committee meeting. *See Serious Neuropsychiatric Adverse Events with Drugs for Smoking*, *Briefing Document*, FOOD & DRUG ADMIN. (Sept. 14, 2016), https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/psychopharmacologicdrugsadvisorycommittee/ucm520103.pdf [https://perma.cc/F2D3-VTAX].

events in patients treated with CHANTIX compared to patients treated with placebo. The four observational studies found that rates of serious NPS AEs in patients taking CHANTIX did not differ from those taking other agents; however, outcomes examined in these studies did not include the full range of NPS AEs that have been reported.

With results from the EAGLES study still two years away, Pfizer considered how it might be able to share the observations from the two meta-analyses and the four observational studies. Although not conclusive, this information had important relevance to prescribers who were weighing the well-established health risks of smoking against the uncertain association between CHANTIX therapy and NPS AEs. Pfizer found no clear path. FDA's restrictions on OLPC limited Pfizer's ability to communicate the results of these six trials. And FDA was unlikely to add the new data to the product label, because the data did not meet the standard of "substantial evidence."

Pfizer discussed these impediments with FDA, and the agency agreed to add information about the meta-analyses and observational studies to the CHANTIX label. This was an expedient solution to the unique circumstances surrounding CHANTIX, but it left unaltered the restrictions that had blocked communications of information that clearly could have benefited physicians, patients, and payors.[60]

C. Subpopulations (Forest Plots)

Published reports of clinical trials—including pivotal trials that are the bases for product approvals—often include "forest plots" that report observed results for study subgroups. Even when these subgroups are small, prescribers may be interested in seeing whether results are consistent across subgroups.

As with observational or retrospective studies, FDA's "substantial evidence" requirement generally excludes subgroup analyses from product labeling and prohibits manufacturers from communicating subgroup analyses. The "consistent with label" draft guidance that FDA issued in January 2017 indicates that information about product experience in subgroups of an approved patient population would be considered to be consistent with a product's approved label.[61] The guidance does not remove the risk of enforcement, however, because it is not legally binding and is expressly subordinate to existing regulations and prior FDA guidance.

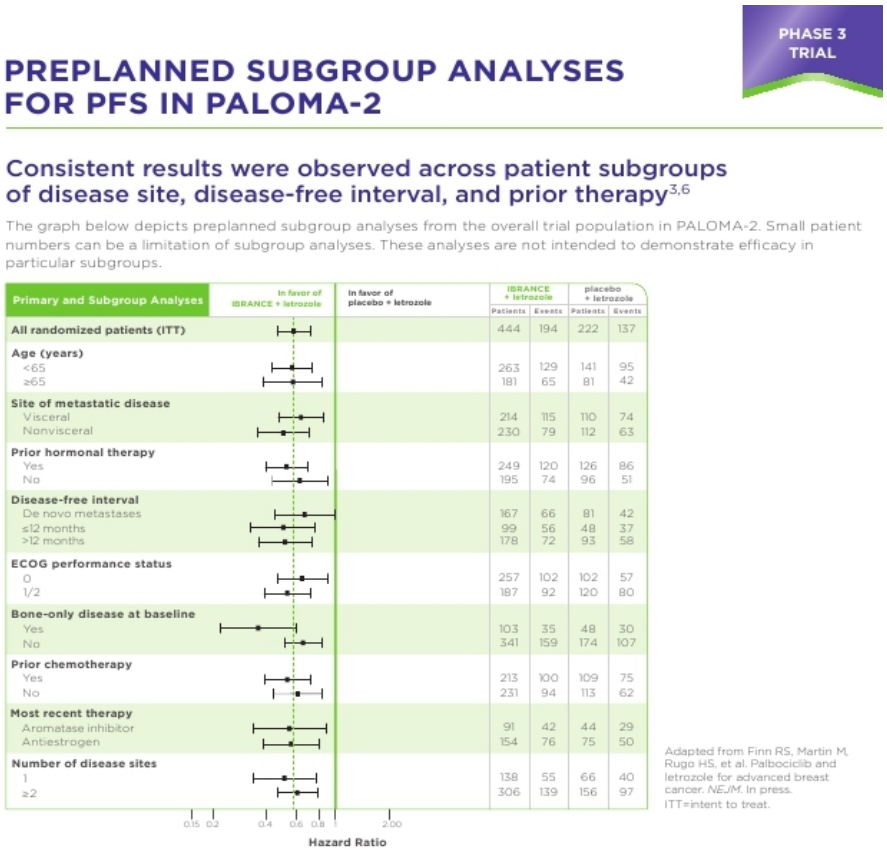
The draft guidance also is not clear on what kind of presentations of subgroup analyses FDA would consider appropriate. The guidance states generally that presentations "should be scientifically appropriate and statistically sound to support the representations or suggestions made in the communication," and "should be accurately characterized . . . ." Fair enough. But FDA often has taken a broad view of

---

[60] In June 2014, FDA issued a draft guidance on manufacturer communications regarding off-label data on risk information that rebuts, mitigates, or refines information in the product label. FOOD & DRUG ADMIN., *Draft Guidance*, *Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products—Recommended Practices* (June 2014). Similar to other guidance on OLPC, this draft guidance largely reinforces, rather than eases, FDA's traditional restrictions on OLPC, and limits the circumstances and manner in which communications may occur. Because the draft guidance does not remove the legal risk of enforcement, it inhibits manufacturer communications. *See* Va. v. Am. Booksellers Assoc., 484 U.S. 383, 392–93 (1988) (noting that the possibility of enforcement causes self-censorship, even when few prosecutions occur).

[61] "CONSISTENT WITH LABEL" DRAFT GUIDANCE, *supra* note 21, at 6.

what a presentation may imply, and a very dim view of the effectiveness of contextual statements,[62] making it very risky for manufacturers to include forest plots in product communications. Pfizer was able to include the forest plot depicted below in its product communications by relying on First Amendment principles.



PHASE 3 TRIAL

PREPLANNED SUBGROUP ANALYSES FOR PFS IN PALOMA-2

Consistent results were observed across patient subgroups of disease site, disease-free interval, and prior therapy[3,6]

The graph below depicts preplanned subgroup analyses from the overall trial population in PALOMA-2. Small patient numbers can be a limitation of subgroup analyses. These analyses are not intended to demonstrate efficacy in particular subgroups.

Primary and Subgroup Analyses	IBRANCE + letrozole Patients	IBRANCE + letrozole Events	placebo + letrozole Patients	placebo + letrozole Events
All randomized patients (ITT)	444	194	222	137
Age (years)				
<65	263	129	141	95
≥65	181	65	81	42
Site of metastatic disease				
Visceral	214	115	110	74
Nonvisceral	230	79	112	63
Prior hormonal therapy				
Yes	249	120	126	86
No	195	74	96	51
Disease-free interval				
De novo metastases	167	66	81	42
≤12 months	99	56	48	37
>12 months	178	72	93	58
ECOG performance status				
0	257	102	102	57
1/2	187	92	120	80
Bone-only disease at baseline				
Yes	103	35	48	30
No	341	159	174	107
Prior chemotherapy				
Yes	213	100	109	75
No	231	94	113	62
Most recent therapy				
Aromatase inhibitor	91	42	44	29
Antiestrogen	154	76	75	50
Number of disease sites				
1	138	55	66	40
≥2	306	139	156	97

Adapted from Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole for advanced breast cancer. *NEJM*. In press.
ITT=intent to treat.

D. Expert Recommendations

Clinical practice often is informed by guidelines and recommendations issued by panels of experts that may vary from or go beyond the information in FDA-approved product labels. These recommendations frequently are considered authoritative in defining appropriate medical care. FDA restrictions on OLPC, however, often create a legal paradox that prevents manufacturers from communicating off-label uses that physicians and insurers widely recognize as standard-of-care.

A telling example of this paradox arose in connection with Pfizer's pneumococcal conjugate vaccine, PREVNAR 13®. FDA initially approved PREVNAR 13 in 2010 for the prevention of invasive disease and otitis media caused by streptococcus pneumoniae in infants and young children six weeks to five years of age. Subsequently, FDA expanded the product's indications to include children between six and 17 years old, and adults 18 and older.

---

62 *See* FDA 2017 MEMO ON OLPC, *supra* note 8, at 29–30 (generally rejecting the effectiveness of contextual statements).

Separately from FDA's product approvals, the federal Centers for Disease Control and Prevention (CDC) published recommendations for use of PREVNAR 13 based on input from its Advisory Committee on Immunization Practices (ACIP). CDC's recommendations establish the medical standard of care for vaccination in the United States and are a prerequisite for coverage by most health insurance providers, private and public.[63] Additionally, licensed health care prescribers generally follow CDC's recommendations. Consequently, prescriber awareness of CDC recommendations is critical to ensuring that individuals are vaccinated appropriately.

In 2010, CDC recommended that PREVNAR 13 be administered to children aged six through 18 with immunocompromising conditions. FDA regulations prohibited Pfizer from sharing this recommendation with prescribers, however, because there were no data, constituting "substantial evidence," establishing the safety and effectiveness of PREVNAR 13 in immunocompromised children.

Consistent with FDA's regulations, Pfizer refrained from sharing ACIP's recommendation with prescribers. In 2013, when Pfizer issued a press release announcing a new indication for PREVNAR 13, it did not make reference to ACIP's 2010 recommendation. This prompted a CDC official to complain to Pfizer that failing to communicate ACIP's recommendation was "misleading." Thus, Pfizer found itself whipsawed by the conflicting communications policies of two federal agencies—both of which reside in the same governmental department.

Recent FDA draft guidance documents—including "Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices," in 2014,[64] and the "Consistent with Label" Draft Guidance in 2017[65]—have not resolved the dilemma that manufacturers face as a result of inconsistencies between FDA and CDC actions.

IV. ELEMENTS OF A NEW REGULATORY APPROACH

The basic legal standard that speech must be truthful and non-misleading in order to enjoy First Amendment protection is particularly important for OLPC because the content and the context of OLPC are inherently complex and have potentially critical impacts on individual and collective health. In keeping with this standard, the best answer to many of the most common objections to broader OLPC is to apply fundamental quality standards. Truthful and non-misleading communications are the touchstone, but in an environment of highly complex medical and scientific information, this basic standard requires some fleshing out.

For instance, clear disclosure of relevant limitations on the underlying data used to support a discussion of an off-label condition of use is essential, so manufacturers should include an adequate description of study design, methodology, and limitations. Broader contextual information may also be necessary to ensure that OLPC can be properly understood and applied. Are there other studies, published or unpublished, that raise important questions or are necessary to properly understand off-label information and its relevance to patient care? Such an approach not only

---

63 *E.g.,* 29 C.F.R. § 2590.715-2713 (2017).

64 FOOD & DRUG ADMIN., *Revised Draft Guidance, Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products — Recommended Practices* (2014).

65 "CONSISTENT WITH LABEL" DRAFT GUIDANCE, *supra* note 21.

honors the fundamental principle of the free flow of information that underlies the First Amendment, but also transcends the paternalism of the current restrictive FDA approach and allows medical professionals to make judgments about the use of medical products based on the most complete and contemporary information.[66]

More work could usefully be done on such standards and their application. Confusion among various labels for such standards—including "substantial evidence," "competent and reliable scientific evidence," "scientifically appropriate and statistically sound"—only underscores the need for clear guideposts in this area.[67] A potentially fruitful source of learnings would be the decades of jurisprudence in Federal Trade Commission cases applying flexible yet rigorous evidentiary standards to health-related claims depending on the nature and strength of the claim in question,[68] as opposed to the current FDA "one-size-fits-all" approach of applying the substantial evidence standard to virtually all OLPC.[69]

The PhRMA/BIO Joint Principles on Responsible Sharing of Truthful and Non-misleading Information About Medicines with Health Care Professionals and Payers provide a helpful start in this direction. The PhRMA/BIO Principles—which are founded upon commitments to science-based communication, to providing appropriate context about data, and to accurate representation of data—are aimed at offering a platform to stimulate and guide discussion of responsible and medically sound OLPC.[70] The Principles are based on three fundamental commitments:

- Commitment to Science-Based Communication: There are many types of data and analyses that are scientifically and statistically sound, and which can help improve patient care. We must increase access to these types of communications.
- Commitment to Provide Appropriate Context about Data: Communications should clearly disclose appropriate contextual information about data that are presented, including limitations on statistical methods and study design, to ensure that health care professionals and payers are clearly informed about emerging data on the safety, effectiveness, and value of medicines.
- Commitment to Tailoring Communications to the Intended Audience: Communications should keep the sophistication of the intended audience in mind to ensure that new information is clearly communicated and incorporated into existing knowledge and expertise.[71]

---

[66] Unfortunately, FDA's January 2017 Memorandum on OLPC adheres to the agency's outdated paternalistic approach. *See* FDA 2017 MEMO ON OLPC, *supra* note 8, at 30 ("If disclosures were the only limitation on a firms' [sic] ability to distribute a medical product for an unapproved use, we are concerned that it would result in a return to an environment where audiences are faced with a large volume of advertising and promotional labeling claims based on conjecture or extrapolation from limited data, most of which is later found to be false and misleading, but not before misinformation is widely circulated and patients are harmed.").

[67] *See* Amarin Pharma, Inc. v. Food & Drug Admin., 119 F. Supp. 3d 196, 221 (S.D.N.Y. 2015).

[68] *See, e.g.,* POM Wonderful v. FTC, 777 F.3d 478, 491 (D.C. Cir. 2015), and cases cited therein.

[69] 21 C.F.R. § 202.1(e)(6) (2008).

[70] PhRMA & BIO, *Principles on Responsible Sharing of Truthful and Non-Misleading Information About Medicines With Health Care Professionals and Payers* (2016), https://www.phrma.org/codes-and-guidelines/principles-on-responsible-sharing-of-truthful-and-non-misleading-information-about-medicines-with-health-care-professionals-and-payers [https://perma.cc/N7N9-SJWF].

[71] *Id.*

Governance is also an area that requires further exploration. Even voluntary standards still need referees and some type of enforcement mechanism. A number of potential resources and processes already exist in this area, including peer review, medical compendia, medical societies, and as a last resort, the courts applying a Lanham Act or other relevant legal regime. Examples also exist of successful self-regulatory processes in the advertising and promotional space, including the National Advertising Division of the Council of Better Business Bureaus and, in the UK, the self-regulatory structure of the Association of the British Pharmaceutical Industry.[72]

CONCLUSION

Broad restraints on OLPC are unconstitutional and detrimental to medical practice. FDA's traditional regime is, quite literally, from a different era and needs to be adapted to modern constitutional law. Instead of persisting in its efforts to bar manufacturers from participating in medical discourse, FDA should enable manufacturers to share accurate, complete, and balanced information that will enhance prescribers' understanding of how medical products may best be used. This means undoing existing governmental prejudices against OLPC and modernizing FDA's regulatory approach.[73]

Does the medical products industry deserve this new chance? And will they live up to the responsibilities that accompany looser restraints on OLPC? The First Amendment unequivocally answers the first question, rejecting paternalistic controls in favor of a free exchange of information.[74] Recent history is instructive on the second question. Many manufacturers, through their own devices and/or as a result of experiences under corporate integrity agreements, now have much stronger controls on OLPC than they did when the spate of off-label enforcement actions began in the early 2000s.[75] And the examples provided in this article demonstrate that manufacturers are capable of sharing beneficial off-label information responsibly.

It should be noted that FDA is not the only governmental entity that needs to reconsider its biases against OLPC. The discriminatory impact of FDA's selective bias against manufacturers has been replicated and amplified by parallel enforcement in other arenas, including *qui tam* litigation under the Federal False Claims Act, state

---

[72] *See also* DUKE-MARGOLIS CENTER FOR HEALTH POLICY, POLICY OPTIONS FOR OFF-LABEL COMMUNICATION: SUPPORTING BETTER INFORMATION, BETTER EVIDENCE, AND BETTER CARE (Feb. 2016) for an interesting discussion of a potential third-party review body for off-label claims analogous to the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices.

[73] An essential first step is for FDA to revoke its categorical ban on OLPC that is not based on "substantial evidence." As illustrated by the examples provided above, this restriction inhibits a wide range of constitutionally protected speech.

[74] Va. St. Bd. of Pharmacy v. Va. Citizens Consumer Council, 425 U.S. 748, 770 (1976) ("[The] choice, between the dangers of suppressing information, and the dangers of its misuse if it is freely available, [is a choice] that the First Amendment makes for us.").

[75] The interest group Public Citizen, which is openly distrustful of pharmaceuticals manufacturers, has observed that financial penalties arising from off-label marketing "declined dramatically" between 2013 and 2015. Public Citizen is skeptical, however, that drug companies have improved their compliance controls. PUBLIC CITIZEN, TWENTY-FIVE YEARS OF PHARMACEUTICAL INDUSTRY CRIMINAL AND CIVIL PENALTIES: 1991–2015 13, 28 (Mar. 31, 2016). Our own experience is that the systems that companies have today for ensuring against improper marketing are far more sophisticated and reliable than they were 10–20 years ago, when most of the major enforcement actions occurred.

government and private actions under state consumer protection laws, claims by payors under RICO or other theories, and private product liability actions. The cumulative effect of this onslaught has significantly deterred manufacturers from chancing even obviously beneficial OLPC.

Increasingly, courts are rejecting all of these styles of assault on OLPC. A consistent body of case law makes clear that state-law restrictions on OLPC—private or governmental—generally are preempted under the FDCA.[76] In federal RICO cases, a growing consensus among courts holds that manufacturers cannot be held liable for sharing off-label information, both because off-label prescribing itself is legal and in light of the attenuated causation between product promotion and patient use.[77] For similar reasons, courts regularly dismiss suits under the False Claims Act,[78] and recent cases applying the Supreme Court's *Escobar* decision[79] suggest that dismissal for lack of materiality is appropriate when the government knowingly reimburses fees and costs for medicines that are prescribed off-label.[80]

The approach to OLPC advocated in this article will, to be sure, still require some degree of regulatory and/or third-party oversight, as well as the exercise of judgment and self-restraint on the part of manufacturers. But as the discussion above indicates, we are past the point where the traditional FDA straitjacket on OLPC can reasonably be defended either on legal or practical grounds. The fact is that we are already moving to a new paradigm, whether the traditionalists like it or not. Instead of resisting this evolution, all stakeholders should collaborate to achieve a workable new structure for OLPC that serves the interests of health care professionals and patients in the free flow of truthful, non-misleading, and meaningful product information.

The biblical parable does not indicate whether the Prodigal Son, upon his return, was a new person or whether he brought home his old ways of profligacy and irresponsibility. This also is not clear for all OLPC by all medical products manufacturers. But many kinds of OLPC—including the examples provided in this Article—are wholly distinct from the reckless opportunism that opponents of OLPC fear. As in the parable, FDA should accept OLPC as a legitimate part of medical commerce and practice, and should regulate it accordingly, instead of banishing it indiscriminately.

---

[76] *See* Chasnow & Levitt, *supra* note 5, at 269 ("[T]he clear teaching of *Buckman*, and the consistent view of lower courts that have addressed restraints on OLPC, is that state-law regulation of OLPC is preempted by federal law.").

[77] *See, e.g.,* Sidney Hillman Health Ctr. v. Abbott Laboratories, Inc. 873 F.3d 574, 578 (7th Cir. 2017) ("[T]here are so many layers, and so many independent decisions, between [off-label] promotion and payment that the causal chain is too long to satisfy the Supreme Court's requirements" for RICO liability) (citing similar rulings from seven other circuits).

[78] *See,* e.g. United States *ex rel.* King v. Solvay Pharm., Inc., 871 F.3d 318, 327–29 (5th Cir. 2017); United States *ex rel.* Booker v. Pfizer, Inc., 847 F.3d 52, 57–59 (1st Cir. 2017).

[79] Universal Health Servs., Inc. v. United States *ex rel.* Escobar*,* 136 S. Ct. 1989 (2016).

[80] *See King*, 871 F.3d at 329 n.9; *Booker,* 847 F.3d at 59 n.7.