



**TIP OF THE ICEBERG II: HOW THE
INTENDED-USES PRINCIPLE
PRODUCES MEDICAL KNOWLEDGE
AND PROTECTS LIBERTY**

Christopher Robertson and Victor Laurion*

* Robertson@email.arizona.edu; Christopher Robertson, JD, PhD is Professor and Associate Dean for Research and Innovation, James E. Rogers College of Law, University of Arizona; Visiting Professor, NYU School of Law (2016-17); Affiliated Faculty, Petrie-Flom Center for Health Law Policy, Biotechnology and Bioethics, Harvard Law School; Affiliated Member, NYU Langone Health Working Group on Compassionate Use and Pre-Approval Access (CUPA). Victor Laurion, MD, completed this work while Resident at Department of Emergency Medicine, Department of Pediatrics, University of Arizona College of Medicine. Maureen Garmon provided excellent library support. Andrew Shepherd, Zachary Forman, Ellen Stark, Joe Radochonski, and Robert Farquharson provided outstanding research assistance. Parts of this article were previously posted on SSRN as part of the companion piece, Christopher T. Robertson, *The Tip of the Iceberg: A First*

ABSTRACT: In recent years, the Food and Drug Administration's pre-market approval process has come under increasing scrutiny as an infringement on liberty and a regulation of speech. In the first part of this symposium contribution, we offer a case study of Seroquel XR, showing how the FDA's premarket approval process—and the restrictions on “off-label” promotion in particular—caused the drug company to produce and disseminate knowledge about safety and efficacy for new uses. The law successfully resolved the collective action problem of producing knowledge, even while the law protected the liberty of individual doctors and patients to use the product in ways that the FDA had not considered.

In the second part of the paper, we show a range of other domains, in which Congress similarly uses the actor's intent, shown by the actor's own speech, to narrowly define proscribed conduct. By tailoring the law in this way, Congress achieves policy goals while minimizing the infringement of liberty. This broad review helps advance our understanding of both food and drug law as well as the First Amendment doctrine. The law's use of speech as evidence of intent can produce knowledge while protecting liberty.

INTRODUCTION

Law typically functions in an *ex post* mode—after a bad outcome occurs, a person may face civil liability or criminal sanctions. In a free market economy, the default assumption is that each person has the liberty to sell stuff without governmental approval.

In contrast, the Food, Drugs, and Cosmetics Act (FDCA) requires that *prior* to selling any drug or medical device, the seller must prove

Amendment Right to Promote Drugs Off-Label (October 12, 2016). 78 Ohio State Law Journal __, 2017, Forthcoming; Arizona Legal Studies Discussion Paper No. 16-19. Available at SSRN: <https://ssrn.com/abstract=2803315>.

to the Food and Drug Administration (FDA) that it is in fact safe and effective.¹ The primary distinction that creates FDA jurisdiction is the seller's intent that the product be used to treat a disease.² And the specific intention matters too: it's one thing if the company intends to cure bladder cancer; another if the company intends to cure macular degeneration.³ Whatever the intention may be, that is what defines the burden of proving safety and efficacy. While a medical product can have multiple intended uses, to avoid criminal liability for selling a "misbranded" product, all those intentions must be disclosed and their safety and efficacy proven.⁴

Once a product is approved for at least one use, physicians are free to prescribe the product "off-label" for other uses as well. Physicians are generally outside the regulatory ambit of the FDA, as long as they are acting independently from the companies selling in

¹ See generally Christopher T. Robertson, *When Truth Cannot Be Presumed: The Regulation of Drug Promotion Under an Expanding First Amendment*, 94 B.U. L. REV. 545 (2014) (reviewing this statutory regime); 21 U.S.C. §§ 321(g)(1)(B)–321(g)(1)(C) (2012) (incorporating the intent concept in the definition of "drug"); 21 U.S.C. § 331 (2012) (prohibiting misbranding acts); 21 U.S.C. § 352 (2012) (defining "misbranding" and labeling requirements); 21 U.S.C. § 333 (2012) (specifying felonies and misdemeanors). Directions for use may be inadequate if "[s]tatements of all . . . uses for which such drug is intended" are omitted. 21 C.F.R. §§ 201.5(a)–201.5(b) (2017). See also 21 C.F.R. § 201.128 (2017) (referring to the "the objective intent of the persons legally responsible for the labeling of drugs" and outlining the evidence that can show such intent).

² 21 C.F.R. § 201.128 (2017).

³ See *Sigma-Tau Pharms. v. Schwetz*, 288 F.3d 141, 145 (4th Cir. 2002) (discussing the Orphan Drug Act amendments to the FDCA, explaining the words "for such disease or condition" suggests Congress intended to make section 360cc "disease-specific, not drug-specific"); *Spectrum Pharms. Inc. v. Burwell*, 824 F.3d 1062, 1067 (D.C., Cir. 2016) (citing *Sigma-Tau Pharms.*).

⁴ See Nathan Cortez, *The Statutory Case Against Off-Label Promotion*, 83 U. CHI. L. REV. ONLINE 124, 131 (2016); see also sources cited, *supra* notes 2-3. See, e.g., *Alberty Food Prods. Co. v. United States*, 185 F.2d 321, 326 (9th Cir. 1950) (holding that a drug product was misbranded because its labeling failed to state the intended use of the drug as suggested by the company in newspaper advertisements).

interstate commerce. Nonetheless, if the company begins to intend additional uses for its product, it must return to the FDA for a “Supplemental New Drug Application,” to show safety and efficacy of those new uses. In fact, roughly half of the applications submitted to the FDA are to seek approval for such new uses of old drugs, essentially bringing off-label uses on-label.⁵

Of course, there is no premarket approval process for other consumer products, like televisions or cars. Why would the law function so differently in the market for drugs and medical devices?

One problem is that it is harder to observe quality (and risk) in this domain. Television shoppers see and hear each model displayed on the wall of the store, and car shoppers can take a test drive. Although it is possible to simply try a drug (typically only after buying it), that experience can be costly and onerous, given the severe side effects that are present in many drugs. For some patients, time may also be essential. The patient may only have one shot at choosing the right drug.

Even when a patient tries a drug, it is not obvious whether the drug has in fact worked, or whether the disease has run its natural course, or whether the patient may have succumbed to the placebo effect. Given the complexity of the human body, the efficacy and safety of a medical product must be investigated systematically. Such investigations are expensive, in terms of both time and money. It would not be sensible or feasible for an individual with cancer to

⁵ Bo Wang & Aaron S. Kesselheim, *Characteristics of Efficacy Evidence Supporting Approval of Supplemental Indications for Prescription Drugs in United States, 2005-14: SYSTEMATIC REVIEW*, 351 *BMJ* h4679 (2015) (“In 2014 the FDA approved 40 new supplemental indications for already marketed drugs, compared with original approvals of 44 novel small molecule and biologic agents during the same period.”).

undertake such original scientific research; the production of that information is a collective action problem.⁶

Even if information about the quality of a drug exists, it is likely not optimally distributed for the making of consumption decisions. In contrast, since the quality of a television is largely transparent to the potential purchaser, he or she can readily ascertain its value in deciding whether to make a trade with the manufacturer (via the retailer) at a given price. In contrast, if anything is known about a medical product, it is likely known by the seller of the product, not the consumer; a classic “information asymmetry.”⁷ The individual patient only knows her own experience with the drug (if any), and her physician may know a few dozen or hundreds more anecdotes. But if a trove of data exists to show that the product is ineffective or dangerous, it is likely in the hands of the seller, who has no incentive to share that information.

The FDCA is the extant regulatory solution to these problems of knowledge production and distribution. The FDCA requires a drugmaker to internalize the cost of scientifically investigating the safety and efficacy of its own product insofar as the drugmaker intends to expropriate value from its product. By putting the burden of proof on drug and device makers who typically hold patents, and thus can reap the profits from proven uses, this regulatory regime produces knowledge which was not produced in the unregulated market that preceded it. With this science, physicians help patients

⁶ See JOSEPH E. STIGLITZ, *ECONOMICS OF THE PUBLIC SECTOR* 79-80 (Ed Parsons ed., 3d ed. 1988) (information is a non-rivalrous and non-excludable public good, which will be insufficiently produced without regulatory intervention).

⁷ See generally Kenneth J. Arrow, *Uncertainty and the Welfare Economics of Medical Care*, 53 *AM. ECON. REV.* 941, 941-73 (1963); Deborah Haas-Wilson, *Arrow and the Information Market Failure in Health Care: The Changing Content and Sources of Health Care Information*, 26 *J. OF HEALTH POL. AND L.* 1031, 1031-44 (2001).

make evidence-based consumption decisions, and drug and device makers compete on proven quality rather than on hype. When this information is produced and released it creates an astute market whereby physicians, patients, and payors can better evaluate whether a product is worth its price.

This limned account does not show that the current FDA approval process is the only way to solve this collective action problem or that its particular instantiation strikes exactly the right balance to maximize aggregate social welfare.⁸ The policy debate should continue. However, in recent years, commentators and courts have sought to short-circuit this debate by arguing that there is a First Amendment *right* for drugmakers to promote their products off-label, without proving the safety and efficacy as the FDA requires.⁹ In this short symposium contribution we do not resolve this debate, but hope to inform it.

In Part I, we provide a case study to illustrate precisely *how* the FDA premarket approval regime produces knowledge. We show that the current regime protects the liberty to use drugs off-label while nonetheless incentivizing companies to invest in science that informs clinical decisions about new intended uses.

Some of the prior discussion of the FDA has suggested that its form of regulation is somehow aberrant or disingenuous; not really a regulation of conduct but rather a cloaked regulation of speech. Part II examines laws in a wide range of other domains—from banking and bribery to guns and mining, which function similarly to

⁸ See, e.g., Richard Epstein, *Against Permittis: Why Voluntary Organizations Should Regulate the Use of Cancer Drugs*, 94 MINN. L. REV. 1, 20 (2009); Cassie Frank et al., *Era of Faster FDA Drug Approval Has Also Seen Increased Black-Box Warnings and Market Withdrawals*, 33 HEALTH AFF. 1453 (2014) (documenting the correlation between false positives and faster review times following Prescription Drug User Fee Act).

⁹ See, e.g., *United States v. Caronia*, 703 F.3d 149, 162 (2012) (quoting *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653, 2659 (2011)).

the FDCA. All these legal regimes seek to protect a liberty to engage in a wide range of conduct done without illicit intent. Nonetheless, these laws criminalize otherwise-legal behavior if done with an illicit intent. Moreover, like the FDA, these other legal regimes routinely use speech as evidence of that intent.

I. HOW THE FDCA'S PRE-MARKET APPROVAL SYSTEM PRODUCES KNOWLEDGE: THE CASE OF SEROQUEL XR

This section describes how the FDA's pre-market approval system promotes the generation of high-quality research, provides a venue for transparent debate, and ultimately leads to the creation of a label that informs clinical practice and patient care.

We show that regardless of the FDA's decision to approve or disapprove of an indication, the process itself yields valuable public goods. To illustrate this point, we use AstraZeneca's petition to expand the label for Seroquel XR, a medication initially marketed to address severe psychiatric illness such as schizophrenia or bipolar disorder. At a single point in time, Seroquel XR was up for label expansion into both generalized anxiety and major depressive disorders. The label was ultimately expanded to include limited use in depression, but not expanded to on-label use in anxiety, despite the efforts of AstraZeneca to prove its efficacy and safety for both conditions. The process caused much to be learned about the drug's uses in both depression and anxiety. We begin by explaining why the Seroquel case is particularly relevant to those concerned with off-label use.

Seroquel belongs to a class of medications termed 'second-generation antipsychotics.' These medicines alter the actions of neurotransmitters in the brain to treat psychosis and regulate mood. Second-generation antipsychotics are considered safer than first-generation drugs, which causes them to be more broadly used. As a result, Seroquel and other second-generation antipsychotics permeated clinical practice in ways that the first-generation drugs never could. Whereas first-generation antipsychotics found difficulty

gaining traction outside of severe mental illness because of the risk of extrapyramidal side effects (muscle spasm, contraction, and restlessness), second-generation drugs have enjoyed a much greater flexibility in prescribing practices among practitioners – much of it done off-label.

Rampant off-label prescribing of Seroquel was documented in a 2008 article in the journal *Pharmacotherapy*.¹⁰ To build a list of drugs where off-label prescribing was particularly worrisome, the authors assigned priority based on the volume of off-label use, the safety of the drug, and a third composite factor that synthesized cost, tenure of the drug, and the degree to which it was marketed. Quetiapine (the generic name for Seroquel) topped the list. The study went on to describe the most common off-label uses for Seroquel: bipolar maintenance, depression, and anxiety.

As explained above, off-label use is perfectly legal, but if AstraZeneca promoted those uses, it would reveal an illegal intent. Indeed, that may have happened. In 2010, AstraZeneca paid \$520 million to settle claims from the Department of Justice (DOJ) that the company promoted Seroquel to doctors and hospitals for unapproved uses including anxiety and depression.¹¹ The DOJ alleged that although the drug was approved for schizophrenia and bipolar disorder only, the company promoted the drug to doctors who did not routinely treat such patients. These physicians included those “who treat the elderly, primary care physicians, pediatric and adolescent physicians, and in long-term care facilities and prisons.”¹²

¹⁰ Surrey M. Walton et al., *Prioritizing Future Research on Off-Label Prescribing: Results of a Quantitative Evaluation*, 28 PHARMACOTHERAPY 1443, 1443 (2008).

¹¹ Press Release, U.S. Dep’t of Just., Pharmaceutical Giant AstraZeneca to Pay \$520 Million for Off-label Drug Marketing (Apr. 27, 2010), <https://www.justice.gov/opa/pr/pharmaceutical-giant-astrazeneca-pay-520-million-label-drug-marketing> (last visited Oct. 9, 2017).

¹² *Id.*

The company allegedly sponsored doctors to promote additional uses in speakers' bureaus and continuing medical education (CME) programs, so that other doctors would prescribe accordingly. The DOJ alleged that the company even hired ghostwriters to publish supporting articles authored by doctors who did not actually participate in these studies. Because these activities revealed AstraZeneca's intent that its drug be used for ways not approved on its label, the products arguably became misbranded under the FDCA. On the Government's theory, selling such a misbranded drug under the Medicare and Medicaid programs constituted "false claims," creating a large financial corpus for recovery, and putting enormous pressure on the company to settle.

This potential liability for off-label promotion was well known to AstraZeneca and the broader pharmaceutical industry. So, even while allegedly promoting off-label, AstraZeneca invested in clinical trials to study these broader uses, with the goal of eventually petitioning the FDA to approve Seroquel XR for major depressive disorder and generalized anxiety disorder. AstraZeneca submitted that Supplemental New Drug Application on February 27, 2008, and spent nearly two years attempting to persuade the FDA that the scientific literature supported the safety and efficacy of those new uses. An examination of the medical literature around the time of this application reveals the ways in which this regulatory process produces knowledge about these new uses.

In 2010, Cochrane, medicine's most rigorous and well-regarded source for meta-analysis of scientific studies, released a pair of formal reviews of the literature on the use of second-generation

antipsychotics for depression¹³ and anxiety.¹⁴ As Figure 1 illustrates, studies on Seroquel (quetiapine) dominated the anxiety literature and were well-represented in the depression literature. Of the eleven studies reviewed for generalized anxiety, seven dealt with Seroquel and again all seven were sponsored by AstraZeneca. Of the twenty-eight studies included in the review for depression, seven dealt with Seroquel and all seven were sponsored by AstraZeneca. All fourteen studies were published between 2006 and 2009.

Beyond the Cochrane Reviews—which focused only on the highest-quality studies—we also extracted data from PubMed using title and abstract searches for "quetiapine + depression", "quetiapine + anxiety". The number of such publications each year is plotted in Figure 2. It appears that overall publication velocity on quetiapine for depression and anxiety increases into the FDA's 2009 review process. Such a trend may illustrate an increased interest from scientists, clinicians, and journal publishers in investigating the drug's use for these purposes, as well as AstraZeneca's own efforts to fund and conduct such studies, with the goal of persuading the FDA that the product is safe and effective for those uses.

¹³ Katja Komossa et al., *Second-Generation Antipsychotics for Major Depressive Disorder and Dysthymia*, COCHRANE DATABASE OF SYSTEMATIC REVIEWS 2010, Issue 12. Art. No.: CD008121. DOI: 10.1002/14651858.CD008121.pub2.

¹⁴ Anna M Depping et al., *Second-Generation Antipsychotics for Anxiety Disorders*, COCHRANE DATABASE OF SYSTEMATIC REVIEWS 2010, Issue 12. Art. No.: CD008120. DOI: 10.1002/14651858.CD008120.pub2.

Figure 1 — Research on Second-Generation Anti-Psychotics for Depression and Anxiety, Appearing in Two 2010 Cochrane Reviews of the Literature, 2006-2009

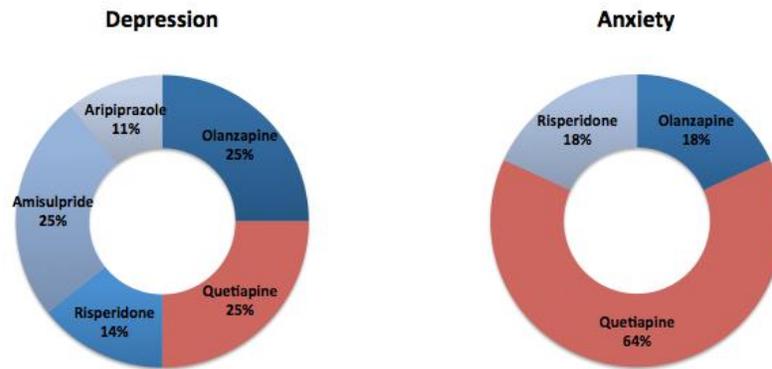
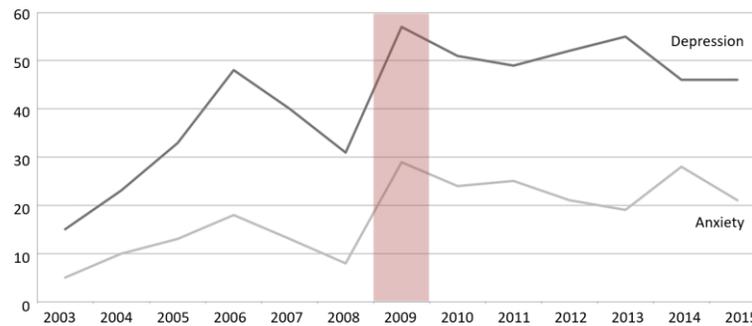


Figure 2 — Publications in the Biomedical Literature with Quetiapine and Depression or Anxiety in Title or Abstract (2003-2015), with FDA Review of Seroquel XR Highlighted



In December of 2008, while AstraZeneca's February 2008 application was pending, the FDA exercised its discretion to refer the matter to an advisory committee.¹⁵ The regulators asked for input on two questions:

1. What are the public health consequences of expanding the use of Seroquel XR into a much larger psychiatric population with MDD [major depressive disorder] and GAD [generalized anxiety disorder]?
2. In particular, how should less well-defined concerns about longer-term metabolic risks, a potential risk for tardive dyskinesia, and a concern for an increased risk of sudden cardiac death be considered in this risk benefit discussion?¹⁶

On April 8, 2009, representatives from AstraZeneca met with the FDA's Psychopharmacologic Drugs Advisory Committee to present their evidence supporting Seroquel XR for depression and anxiety. This meeting created an opportunity for an open-forum dialogue among experts from the drug company, experts from the FDA, and members of the community.

The program began with an industry presentation from AstraZeneca advocating for the label expansion.¹⁷ A development director for the company acknowledged that, "FDA was clear . . . that

¹⁵ U.S. Dep't. of Health & Human Services, Memorandum, Thomas P. Laughren, Director, April 8, 2009 Meeting of the Psychopharmacologic Drugs Advisory Comm. (PDAC) (Mar. 10, 2009), <https://www.fda.gov/ohrms/docets/ac/09/briefing/2009-4424b2-01-FDA.pdf>.

¹⁶ *Id.* at 2.

¹⁷ U.S. Food & Drug Admin., Transcript, Meeting of the U.S. Food and Drug Admin. Ctr. for Drug Evaluation and Research Psychopharmacologic Drugs Advisory Committee (Apr. 8, 2009), <https://www.fda.gov/ohrms/dockets/ac/09/transcripts/2009-4424t2-part1.pdf>.

efficacy had been established in both applications. However, potential metabolic risks and potential risks for tardive dyskinesia [a side effect with involuntary movements of the face and jaw], and sudden cardiac death needed to be discussed."¹⁸

Still, safety must be evaluated in light of efficacy; it is the risk/benefit tradeoff that makes any risk worthwhile. A medical science director for AstraZeneca took the committee through the data that predictably showed the drug to be efficacious for both depression and anxiety. "Quetiapine XR is an efficacious antidepressant consistently reducing levels of depressive symptoms, as monotherapy, as adjunctive therapy in patients with inadequate response, and in elderly patients."¹⁹ Of the studies he presented, only one failed to demonstrate the effectiveness of the drug for depression. For anxiety, all five studies presented by the company demonstrated the effectiveness of the drug. This provided the basis for AstraZeneca's science director to conclude that "quetiapine XR is an efficacious, anxiolytic agent that consistently reduces the level of anxiety symptoms as monotherapy and in elderly patients."²⁰

From there, the focus turned to the more difficult task for quetiapine XR—proving safety. To describe safety concerns for the drug, the company used pooled data from a proprietary database. AstraZeneca's clinical studies database included more than 26,000 patients who took the drug in all study formats. Compare this very large number to the smaller size of the studies reviewed by Cochrane, ranging from n=11 to n=949.²¹ The regulatory process brought to light data from AstraZeneca's proprietary database that otherwise would not be available to physicians and patients. Such large

¹⁸ *Id.* at 15.

¹⁹ *Id.* at 30.

²⁰ *Id.* at 34.

²¹ Cochrane Database, *supra* notes 13-14.

samples are particularly important for evaluating rare adverse events that may be nonetheless severe.

AstraZeneca's analysis of its proprietary data found that the most common adverse events were sedation, somnolence, dizziness and dry mouth. They noted that weight gain was reported more frequently for quetiapine than for the placebo, and found increases in the blood sugar levels of those taking the drug. The levels of HDL (good cholesterol) were also reduced and total cholesterol increased in those taking the drug. On balance, the analysis clearly found a risk of concerning metabolic derangements.

For tardive dyskinesia and extrapyramidal symptoms, AstraZeneca acknowledged that those risks would need to be considered and managed by those who prescribed the medications. On the questions of sudden cardiac death and all-cause mortality, the company's analysis found no higher risk of either with quetiapine than without.

In an effort to moderate the safety concerns, the company's Chief Medical Officer discussed AstraZeneca's intent to continue collecting data and conducting studies in the post-approval phase. He acknowledged that "some risks are present, but these risks are well known, are recognizable to practicing physicians either through physical examination or laboratory testing, and they can be managed."²²

After an opportunity to consider the evidence and ask questions of the company, the advisory committee members undertook a series of votes that would concretely articulate the position of the committee to the FDA. The first set of votes considered effectiveness. The committee found Seroquel XR to be effective as adjunctive therapy for depression by a vote of 9-to-1, and as monotherapy by a vote of 8-to-1 with one abstention. The committee found Seroquel XR

²² Transcript, *supra* note 17 at 73.

to be effective as monotherapy for anxiety by a vote of 7-to-2 with one abstention. As expected, the overwhelming signal was that the medication was effective for both depression and anxiety.

The committee's second set of votes considered safety and the quorum was reduced by one voting member due to an early departure. The committee found Seroquel XR to be acceptably safe as an adjunctive treatment for depression by a less-than-resounding vote of 6-to-3. The summary minutes reflect that, "[t]he committee members who voted yes felt there is a need for adjunctive treatment for patients who have failed previous therapy and the benefit outweighs the risk. For those who voted no believed due to the short-term exposure in the clinical studies, the long-term risk had not been adequately studied."²³

The committee did not find Seroquel XR to be acceptably safe as monotherapy for either depression (0-to-9) or anxiety (0-to-9). As with every vote, the committee members were given an opportunity to explain their positions.

[Psychiatrist:] I voted no. I think the long-term risks of the antipsychotics are greater than I would like to see for metabolic syndrome and risk of dyskinesia for a monotherapy treatment . . .

[Patient representative:] I voted no for very personal reasons, because my son died last summer having schizophrenia with

²³ U.S. Food & Drug Admin., Summary Minutes, Food and Drug Administration Center for Drug Evaluation and Research. Psychopharmacologic Drugs Advisory Committee Meeting 6 (Apr. 8, 2009), <https://wayback.archive-it.org/7993/20170403224146/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM198219.pdf>.

sudden cardiac death, and Seroquel was part of his cocktail. So I'm voting no

[Cardiologist:] I voted no. I was impressed at the discussion around how large the potential patient population to be treated was, the broad use that these drugs might see, and what I felt was the insufficient evidence regarding long-term chronic safety

[Epidemiologist:] I voted no because of the risk-benefit in this large population. It was not favorable

[Consumer Representative:] I voted no out of patient concerns

[Psychiatrist and acting chair:] I voted no. I saw no clear advantage demonstrated in efficacy. There are side effects that we discussed with some unknown risks and consequences. Also, unintended consequences. I was concerned about the wide-scale use of the medication in various settings

[Endocrinologist:] I voted no because I think there are safer alternatives for primary therapy

[Biostatistics Professor:] I voted no because the benefit from efficacy is pretty modest when you balance that against the kind of known risk and the potential risk

[Psychiatrist and researcher:] I voted no. This is an area where there are a lot of other first-line treatments, and I didn't think that the safety profile warranted being among them.²⁴

²⁴ Transcript, *supra* note 17, at 295-97.

The committee did, however, show some flexibility for certain instances (e.g., failure of previous treatments) where monotherapy for depression could be warranted (vote of 4-to-4 with one abstention). When considering the same question for anxiety, the committee voted 2-to-6 against, with one abstention.

In summary, the committee did not find Seroquel XR to be unquestionably safe. In fact, when it came to safety, the only contexts in which the committee was marginally comfortable were those where the drug would be used as adjunctive therapy for depression, or in certain circumstances, for the treatment of depression.

In December 2009, in accordance with the recommendations of the committee, the FDA relabeled Seroquel XR to include an indication for adjunctive treatment in major depressive disorder. There was no expansion for the treatment of generalized anxiety.

Additionally, the FDA updated the label to include new and more robust warnings as elucidated by the review process.²⁵ Weight gain, which was listed on the 2008 label as one of many adverse reactions, was elevated to the level of a 'warning and precaution' in the 2009 labeling. It was noted that "patients should receive regular monitoring of weight."²⁶ The warning for hyperlipidemia was expanded to include robust clinical trials data, recommendations for lipid monitoring while on the drug, and an unmistakable phrase on the first page of the label: "undesirable alterations in lipids have been observed."²⁷ A newly-added warning for increased blood pressure in children and adolescents was provided with accompanying recommendations. New and clarifying warnings for hyperglycemia, hypothyroidism, hyperprolactinemia, potential cognitive and motor

²⁵ Full FDA labeling for Seroquel XR in 2008 and 2009 is available at www.fda.gov, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022047Orig1s011.pdf.

²⁶ *Id.* at p1.

²⁷ *Id.*

impairment, and suicide were also furnished. In total, to measure progress with a crude albeit illustrative statistic, the 'warnings and precautions' section of the label grew from roughly 3,200 words and 1 table in 2008, to approximately 4,000 words and 9 tables in 2009.

This regulatory episode may not have been a complete victory for AstraZeneca, but it was in many respects a victory to those providers and patients considering Seroquel for depression or anxiety. Although healthcare providers could use the drug for these purposes, both before and after AstraZeneca's efforts to expand the labelled indication, the regulatory gauntlet produced a wealth of new information. After 2009, providers were able to reference not just the new label, but also the results of several studies that were likely commissioned for this purpose, analyses of the company's proprietary database, and the recommendations of the expert committee who synthesized all of this information. The FDA approval process effectively produced and compiled information for providers and patients that was significantly better than what was available before.

Some have suggested that if off-label usage is worrisome, then rather than regulate company promotion, Congress should simply prohibit physicians from prescribing off-label. However, the Seroquel episode also illustrates how the regime preserves liberty and individualized choice, which can enhance welfare while also maintaining incentives for companies to produce and reveal information. Physicians could use Seroquel XR for major depressive disorder, even prior to the company's petition to the FDA. Thus, thousands of patients may have benefited from those off-label uses, which turned out to be worthwhile upon later review. Those benefits would not have been captured if off-label prescriptions were made illegal.

Physician discretion is valuable, and especially so when informed by the scientific literature. Risks that have been observed for the median patient may be less relevant for an individual patient without a predisposition to that risk. For example, someone with excellent fasting glucose numbers and cholesterol profile may not be

deterred by Seroquel's risks in those areas, if the medicine is able to manage their intractable anxiety. These are decisions that are best made at the patient-and-provider level with full visibility into both the circumstance of the patient and the best available information on the drug. The FDA's premarket approval system works to inform the latter and give doctors and patients access to the information they need to make better recommendations for the individual patient.

We should pause to acknowledge the limitations of our case study. First, we take at face value the advisory committee's recommendation to approve Seroquel as an adjunctive treatment in major depressive disorder. Others may read the underlying scientific literature to argue in favor of the anxiety indication as well, or against both indications.

Second, any such description of a single case (i.e., an anecdote) cannot itself claim generalizability to other cases; that requires a step of inference based on the commonalities of the cases. To the extent that this case does display structural features common to other cases (e.g., companies acting rationally to produce scientific information when required to do so as a condition of securing a broader market), we can expect to see similar results. Our case study method also does not allow us to observe the counterfactual. The large number of rigorous studies funded by the company prior to seeking FDA approval (as shown in Figure 1), and the accelerating pace of publication immediately prior to seeking that approval (as shown in Figure 2) suggest that the science was produced *because of* the FDA's requirement to prove safety and efficacy for the new intended uses. The \$520 million sanction paid by the company for not previously seeking that FDA-approval is further evidence of the company's incentive to do so going forward. However, it is possible that some of this science would have been produced and released regardless of the FDA's demand for science to support the new indications.

We also do not observe the counterfactual in another sense. If AstraZeneca had been free to (more aggressively) promote its drug for both depression and anxiety years earlier, how many patients would have gotten the worthwhile prescription for depression or the

worrisome prescription for anxiety, and what might have been the overall welfare effects? That counterfactual analysis would also have to embrace the decades of subsequent patients whose physicians would never have received the vast information produced by AstraZeneca in pursuit of an expanded label, which would then help the physicians sort the wheat from the chaff. In principle, this function of prospectively producing information may vastly outweigh the effects on individual patients who do not receive the benefit of company marketing.

II. OTHER INTENT-BASED STATUTES THAT SIMILARLY RELY ON SPEECH EVIDENCE

We have shown in the prior section how the FDCA protects a liberty to use drugs off-label, even while producing knowledge about whatever uses the company does intend. The statute does so by prohibiting marketing of intended uses that have not prevailed through the FDA review process. But what uses are “intended” by the company? Logically, the FDA and prosecutors rely on the speech of drugmakers themselves to reveal their own intent. For example, if a sales representative tells a doctor that Seroquel XR is a great treatment for anxiety, that statement reveals that the company’s agent intends that the drug be used for anxiety.

The FDCA’s misbranding statute can seem peculiar, because it uses the drugmaker’s own speech as evidence of its intended uses for drugs, and then makes it illegal to sell the drugs without approved labelling based on proof of safety and efficacy. Courts and commentators have simply assumed that this is a disguised regulation of speech, and thus an infringement on the liberty of company speakers and on the liberty of patients to make medical

decisions on the basis of those promotions.²⁸ If this conception were accurate, it would bode poorly for the constitutionality of the FDCA.²⁹

To the contrary, in this Section we show that the FDA's form of regulation is not all that peculiar. The law quite often considers certain behaviors perfectly legal, but proscribes them if done with an impermissible intention. Moreover, the law routinely allows that the intention (a state of mind) can be proven through the actor's own speech (speaking her mind) as evidence. As Richard Epstein has explained, "the legal system could not operate if the external evidence of these mental states was systematically excluded from evidence, which of course it is not."³⁰ Reviewing examples from virtually every area of the law, this Section shows that the FDCA's use of speech as evidence of intent is not at all unusual. And, such an

²⁸ See, e.g., Coleen Klasmeier & Martin H. Redish, *Off-Label Prescription Advertising, the FDA and the First Amendment: A Study in the Values of Commercial Speech Protection*, 37 AM. J.L. & MED. 315, 352 (2011) (calling it "disingenuous" to suppose that this is a regulation of conduct rather than speech); *United States v. Caronia*, 703 F.3d 149, 161 (2012).

²⁹ See e.g., *Sorrell v. IMS Health Inc.*, 564 U.S. 552, 577 (2011) ("[T]he State may not seek to remove a popular but disfavored product from the marketplace by prohibiting truthful, nonmisleading advertisements"); *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 374 (2002) (the Court has long "rejected the notion that the Government has an interest in preventing the dissemination of truthful commercial information in order to prevent members of the public from making bad decisions with the information"); *Va. State Bd. of Pharmacy v. Va. Consumer Council, Inc.*, 425 U.S. 748 (1976) (state could not limit pharmacists' advertising of drug prices).

³⁰ RICHARD EPSTEIN, *THE CLASSICAL LIBERAL CONSTITUTION* 438 (2014). See generally KENT GREENAWALT, *SPEECH, CRIME, AND THE USES OF LANGUAGE* 6-7 (1989) (reviewing many such crimes that involve language). See, e.g., *Wisconsin v. Mitchell*, 508 U.S. 476, 489 (1993) ("The First Amendment . . . does not prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent. Evidence of a defendant's previous declarations or statements is commonly admitted in criminal trials subject to evidentiary rules dealing with relevancy, reliability, and the like.").

intent-based test often allows the law to regulate less, and protect liberty more, than an intent-blind statute otherwise would.

First, the intended uses principle is woven throughout food and drug law; it is not merely in the premarket approval requirement for proof of safety and efficacy.³¹ For example, by giving exclusive marketing rights to companies that invest in scientific research on rare diseases, the Orphan Drug Act creates incentives to develop new indications for drugs in those domains.³² However, to strike the right balance between innovation and affordability, the statute's exclusivity applies only to the intended use supported by evidence, approved by the FDA, and shown on the label.³³ The exclusivity does not prevent other companies from making a generic version of the same product to begin competing and driving down prices for other intended uses.³⁴ Unsurprisingly, "intent may be shown by 'labeling claims' or other statements by drug manufacturers."³⁵

A direct analogy can also be found in patent law, where we similarly want to protect liberty and competition in a robust market while also tailoring incentives for knowledge production. Accordingly, generic manufacturers can be liable for inducing others to infringe by using a product in a way that is covered by an inventor's use-patent. Here, Congress has adopted a specific-intent test, rather than predicating liability on mere knowledge.³⁶ In a

³¹ See e.g., *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 142 (2000) ("A fundamental precept of the FDCA is that any product regulated by the FDA -- but not banned -- must be safe for its *intended* use.") (emphasis added).

³² 21 U.S.C. §§ 360aa-360ee (2012).

³³ 21 C.F.R. § 314.94(a)(8)(iv) (2017).

³⁴ See *Spectrum Pharms. Inc. v. Burwell*, 824 F.3d 1062 (D.C., Cir. 2016).

³⁵ *Id.* at 1068 (citing 21 C.F.R. § 201.128).

³⁶ See *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1364 (Fed. Cir. 2003) ("mere knowledge of possible infringement by others does not amount to inducement; specific intent and action to induce infringement must be proven."); See also *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006) (en banc in relevant part)

pivotal case, the Supreme Court has said, “advertising an infringing use . . . show[s] an affirmative intent that the product be used to infringe, and . . . that infringement . . . overcomes the law’s reluctance to find liability when a defendant merely sells a commercial product suitable for some lawful use.”³⁷ Indeed, the illegal intent is often shown by speech, including product instructions and advertisements.³⁸ Yet no court has held that this practice violates the First Amendment.³⁹

In the pharmaceutical domain, for example, although the patent on the chemical compound gabapentin had expired, Warner Lambert also owned a patent on the *use* of gabapentin for certain neurodegenerative diseases, including Alzheimer’s.⁴⁰ TorPharm sought to market the drug for epilepsy but would infringe the Warner Lambert patent if they induced physicians to prescribe gabapentin for one of the patented uses. To determine whether TorPharm had done so, the court looked to whether it had a sales force, published advertisements in medical journals, directly marketed to physicians, funded research, or funded meetings on the

(inducement of infringement under section 271(b) requires a “specific intent” to infringe).

³⁷ *MGM Studios, Inc. v. Grokster, Ltd.*, 545 U.S. 913, 936 (2005) (citation and footnote omitted).

³⁸ See *Lucent Tech., Inc. v. Gateway, Inc.*, 580 F.3d 1301, 1322-23 (Fed. Cir. 2009) (relying on documentation provided with the product); *i4i Ltd. P’ship v. Microsoft*, 598 F.3d 831, 851-52 (Fed. Cir. 2010) (relying on “online training and user support resources”); *Advanced Software Design Corp. v. Fiserv, Inc.*, 641 F.3d 1368, 1376 (Fed. Cir. 2011) (relying on instructions made to customers).

³⁹ *But see Intellectual Ventures I LLC v. Symantec Corp.*, 838 F.3d 1307, 1322 (Fed. Cir. 2016) (Mayer, J., concurring) (“Patents, which function as government-sanctioned monopolies, invade core *First Amendment* rights when they are allowed to obstruct the essential channels of scientific, economic, and political discourse.”).

⁴⁰ See generally *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348 (Fed. Cir. 2003).

claimed method all forms of speech.⁴¹ No First Amendment right was invoked.

It would be ironic if, in the pharmaceutical industry, innovator-companies (like Warner Lambert, since acquired by Pfizer) successfully pled the First Amendment to give them a right to market *off-label*, but when they become plaintiffs in patent cases, were unable to enforce their use-patents because generic makers (like TorPharm) claimed a First Amendment right to promote *on-label* in ways that infringed the innovator's patent.⁴² These two laws have a common goal. Patent law's prohibition on the marketing of infringing uses and the FDCA's prohibition on the marketing of unapproved uses both create incentives for the production of scientific knowledge.⁴³

Beyond the food and drug domain, consider employment discrimination law. Although policymakers may be tempted to interfere with the market in innumerable ways, the background law in most states is one of at-will employment and freedom of contract, allowing an employer to dismiss a worker for any reason or no reason at all. However, an employer violates federal law if it dismisses an employee with the intent to discriminate against her on account of race, sex, age, religion, national origin, or other protected

⁴¹ *Id.*

⁴² See, e.g., *Allergan, Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322, 1331 (Fed. Cir. 2003) (on-label use will support inducement liability); *Acorda Therapeutics Inc. v. Apotex Inc.*, 2011 U.S. Dist. LEXIS 102875, 56 (D.N.J. Sept. 6, 2011), *aff'd* 476 F. App'x 746 (Fed. Cir. 2012) (defendant did not induce infringement where non-infringing uses were approximately 75%); *Wyeth v. Sandoz, Inc.*, 705 F. Supp. 2d 508, 521 (E.D.N.C. 2010) (grant of summary judgment of induced infringement because the "label provide[d] instructions for and encourage[d] direct infringement, thereby establishing the requisite intent for active inducement of infringement").

⁴³ See Robertson, *supra* note 1, at 558-65; Robertson, *Tip of the Iceberg*, cited in the author's note.

bases.⁴⁴ It goes without saying that an employer's speech—e.g., a business plan that describes the profile of employees that the company seeks to retain—could be evidence of this discriminatory intent.⁴⁵ Similarly, in labor law, for certain violations, an employer is only liable if their actions were motivated by an anti-union intent.⁴⁶ Although unlawful intent can be inferred from conduct, it can also be proven by specific evidence, such as an email or other form of speech.⁴⁷

There is, of course, an important liberty interest in saying offensive things, even if those statements are racialized. Yet, hate crime legislation recognizes that the same conduct (e.g., battery) can

⁴⁴ 42 U.S.C. § 2000e-2 (2012). See *Mitchell*, *supra* note 31, at 487 (“In *Hishon v. King & Spalding*, 467 U.S. 69 (1984), we rejected the argument that Title VII infringed employers' First Amendment rights.”).

⁴⁵ See, e.g., *Machinchick v. PB Power, Inc.*, 398 F.3d 345, 349 (5th Cir. 2005) (age discrimination case depended on “a business plan in which [the defendant] described as one of its competitive advantages its intention to ‘hand-pick employees whose mindset resides [sic] in the 21st Century . . .’”); *Price Waterhouse v. Hopkins*, 490 U.S. 228, 251 (1989) (stereotyped remarks are relevant evidence of an employer's motive).

⁴⁶ See *Radio Officers' Union v. NLRB*, 347 U.S. 17, 43 (1954) (“The relevance of the motivation of the employer in such discrimination has been consistently recognized under both 8 (a)(3) and its predecessor.”). The analysis is distinct for other sorts of violations. See Rebecca Hanner White, *The Statutory and Constitutional Limits of Using Protected Speech As Evidence of Unlawful Motive Under the National Labor Relations Act*, 53 OHIO ST. L.J. 1, 3 (1992) (“Both section 8(c) and the First Amendment protect an employer's right to campaign against the union. While coercive speech and conduct by an employer are prohibited by the NLRA, the expression of noncoercive views, arguments, and opinions for and against unionization cannot be held unlawful. Section 8(c), moreover, provides that such protected speech shall not be evidence of an unfair labor practice.”).

⁴⁷ See, e.g., *Moore-Duncan ex rel. N.L.R.B. v. Aldworth Co., Inc.*, 124 F. Supp.2d 268, 282 (D.N.J., 2000) (“[employer] told the employees that a blank sheet would be where they would start during the bargaining process if the union were selected, i.e., with nothing...use of this metaphor provides reasonable cause to believe that the tone of these meetings was coercive.”); see also *AP v. NLRB*, 301 U.S. 103, 132 (1937) (“The publisher of a newspaper has no special immunity from the application of general laws.”).

be punished more severely if done with an illicit motive. Here, the Supreme Court has addressed the First Amendment question directly, finding that speech may serve as evidence of that illicit intent.⁴⁸ The court relied on a WWII-era case holding similarly that under the treason statute, prosecutors could use speech to show proof of motive.⁴⁹

Candidates for public office are allowed to receive gifts from friends and relatives, such as a free week in a beach house or a campaign contribution. These are important liberties, some of which are protected by the Constitution.⁵⁰ However, if a benefactor gives the thing of value with the corrupt intent that it be part of an exchange for an official act, the benefactor has committed a felony.⁵¹ The bribery trial of Illinois Governor Rod Blagojevich depended heavily on his own speech as evidence, whether recorded as wiretaps or given in open court as testimony.⁵²

Similarly, there is an important liberty interest in free travel, locally and across state lines.⁵³ However, under the Mann Act, the same behavior can be felonious, if done with the purpose of illegal sex or prostitution.⁵⁴ It may not always be clear why someone took a

⁴⁸ See *Wisconsin v. Mitchell*, 508 U.S. 476 (1993).

⁴⁹ *Haupt v. United States*, 330 U.S. 631, 642 (1947).

⁵⁰ See generally Christopher T. Robertson et al., *The Appearance and the Reality of Quid Pro Quo Corruption: An Empirical Investigation*, 8 J. OF LEGAL ANALYSIS 375 (2016) (describing the First Amendment doctrine protecting campaign contributions as speech).

⁵¹ 18 U.S.C. § 201(b)(1) (2012).

⁵² *United States v. Blagojevich*, 794 F.3d 729, 743 (7th Cir. 2015).

⁵³ See *Saenz v. Roe*, 526 U.S. 489, 500 (1999) (“The ‘right to travel’ ... protects the right of a citizen of one State to enter and to leave another State, the right to be treated as a welcome visitor rather than an unfriendly alien when temporarily present in the second State, and, for those travelers who elect to become permanent residents, the right to be treated like other citizens of that State.”).

⁵⁴ 18 U.S.C. § 2421 (2012).

child into another state, but if the prosecutors can produce an email offering the child to a sex predator, then those forms of speech would be excellent evidence of the relevant criminal intent.⁵⁵

The banking system also depends on an intent-based test to maintain financial liberty and the liquidity of money, while still monitoring criminal activity and money-laundering in particular. Thus, while it is perfectly legal to make a \$9,500 deposit in the bank in January and another \$9,500 deposit in February, if these two deposits were structured in this way, with the intent to avoid disclosing a \$19,000 deposit, then the depositor has committed a federal felony.⁵⁶ The defendant's own speech, e.g., telling a bank teller to put false names in records, is excellent evidence of that criminal intent.⁵⁷

One could imagine a legal system that required all gun sales to be handled by a dealer who provided robust documentation and background checks, but our current regime favors a more libertarian approach that also tolerates private sales. Accordingly, it is perfectly legal for a person to buy a gun from a dealer, and perfectly legal for the buyer to sell it to another private party. However, if a person purchases a gun with the intent to resell it, without a dealer's license and without documenting the subsequent sale as a dealer, then one commits a federal felony ("straw purchasing").⁵⁸ Testimony showing

⁵⁵ See, e.g., *United States v. Jones*, 748 F.3d 64, 65-66 (1st Cir. 2014) (Mann Act prosecution depending heavily on the defendant's own speech in internet websites and chatrooms).

⁵⁶ See 18 U.S.C. § 371 (2012); 31 C.F.R. § 103.22(a) (2017).

⁵⁷ See, e.g., *United States v. Puerto*, 730 F.2d 627, 631-32 (11th Cir. 1984) (prosecution relying heavily on the defendant's own speech to a key government witness).

⁵⁸ 18 U.S.C. § 922 (requiring the gun seller to collect name and address of buyer and criminalizing false statements in connection with a gun purchase); *Abramski v. U.S.*, 134 S. Ct. 2259 (2014) (Conviction of a defendant upheld based on his own speech that he was the "actual transferee/buyer" of a firearm, despite purchasing the firearm for his uncle).

that a defendant expressed a plan to buy the gun for another person is excellent evidence of that criminal intent.⁵⁹

One could imagine an even more draconian system for illicit drugs, one that prohibited activities that could even possibly facilitate illicit drug use. Instead, current law allows people to manufacture and sell small pieces of pipe and tiny bowls with holes on the side matching that pipe. However, it is a crime to sell drug paraphernalia across state lines, and the definition of that contraband is its intended use.⁶⁰ Thus, the seller of tiny pipes and tiny matching bowls should be unsurprised if federal agents knock on its door shortly after the seller advertises a “420 Blowout Sale.”⁶¹

Under antitrust laws, it is perfectly legal for two competitors to cause a third competitor to fail; that is often an expected and worthwhile phenomenon in a free market. However, if the competitors form a horizontal conspiracy with the intent of driving out the third company, they commit a crime.⁶² The Supreme Court explains that “it is well settled that acts which are in themselves legal lose that character when they become constituent elements of an unlawful scheme.”⁶³ So, if a trade association publishes multiple stories in its industry journal and circulates a memo expressly advocating for members to coordinate their efforts to shut down a

⁵⁹ See, e.g., *United States v. Moore*, 109 F.3d 1456, 1459 (9th Cir. 1997) (upholding conviction where defendant “conceded that the only reason he was in the pawnshop was ‘to stand in for Bobby to get that gun.’”); *United States v. Lawrence*, 680 F.2d 1126, 1127 (6th Cir. 1982) (Store employees’ overhearing of purchaser’s intent to resale used in evidence).

⁶⁰ 21 U.S.C. § 863(d) (2012) (“any equipment . . . primarily intended or designed for use in . . . introducing into the human body a controlled substance . . .”).

⁶¹ *United States v. Assorted Drug Paraphernalia*, 90 F. Supp. 3d 1222, 1225 (D.N.M. 2015) (the 420 Blowout Sale case, recognizing that “420” is code for marijuana).

⁶² See 15 U.S.C. § 1 (1994).

⁶³ *Cont’l Ore Co. v. Union Carbide & Carbon Corp.*, 370 U.S. 690, 707 (1962).

particular type of competitor, then those forms of speech may serve as excellent evidence of an illegal intent.⁶⁴

Similarly, securities law makes it generally permissible for one company to buy another company's stock. Such cross-ownership can serve to hedge risk, for example. However, if a stock-buyer does so with the intent of controlling or merging with the target company, then the buyer is required under the Williams Act to disclose that intention.⁶⁵ Corporate speech contained in internal documents can evince that undisclosed intent.⁶⁶

Tax law also relies on intent and speech as evidence. For example, when determining whether something is a gift, for federal income tax purposes, the courts look to the transferor's own intent.⁶⁷ Similarly, the tax evasion statute allows that individuals may fail to pay what they owe to the IRS, making errors in their own favor. However, a person commits a felony, if he "willfully" refuses to pay what he owes, where "willfully" is defined as "voluntary, intentional violation of a known legal duty."⁶⁸ Many more specific tax statutes disallow a deduction or dishonor a transaction if "the [or a] primary

⁶⁴ See *Alvord-Polk, Inc. v. F. Schumacher & Co.*, 37 F.3d 996, 1007-08 (3d Cir. 1994) ("[I]n assessing whether a trade association (or any other group of competitors) has taken concerted action a court must examine all the facts and circumstances to determine whether the action taken was the result of some agreement, tacit or otherwise . . ." and relying on various trade publications and a memo that was circulated in the industry as evidence thereof); See also *Associated Press v. United States*, 326 U.S. 1, 7 (1945) (First Amendment did not immunize newspapers from Sherman Act).

⁶⁵ See, e.g., *Otis Elevator Co. v. United Techs. Corp.*, 405 F. Supp. 960 (S.D.N.Y. 1975) (Internal documents used to show purchasing company had failed to state an intention to purchase target company for purchase of merger.).

⁶⁶ See *id.*

⁶⁷ See *Comm'r. v. Duberstein*, 80 S. Ct. 1190 (1960).

⁶⁸ See OFFICE OF CHIEF COUNSEL, CRIMINAL TAX DIV., INTERNAL REVENUE SERV., TAX CRIMES HANDBOOK 9 (2009), https://www.irs.gov/pub/irs-utl/tax_crimes_handbook.pdf.

purpose of the transaction is tax avoidance.”⁶⁹ The proof sometimes involves smoking gun internal memos or admissions made during discovery or trial.⁷⁰

Federal mining law also depends on an intent-based test. Federal lands are considered an "open source" and the discoverer of a valuable mineral deposit has a valid claim against the United States government, which allows him to operate a mine on government land.⁷¹ If the defendant is instead on the record as saying that he “could live in the mountains for free by simply doing a nominal amount of assessment work each year,” his own speech may well be used against him to show bad faith, which defeats the claim on Federal lands.⁷²

The primary function of bankruptcy law is to allow individuals to discharge debts and get a fresh start. However, certain debts are not dischargeable, including any debt “for willful and malicious injury by the debtor.”⁷³ Courts must thus determine whether there was an “intentional act the purpose of which is to cause injury or which is substantially certain to cause injury.”⁷⁴ The debtor’s own

⁶⁹ See 26 U.S.C. § 7201 (1982); 26 U.S.C. § 269 (2014) (providing for the disallowing of deductions or credits when the primary purpose for the acquisition of a company is to evade taxation).

⁷⁰ *Vulcan Materials Co. v. United States*, 446 F.2d 690, 696 (5th Cir. 1971) (“if the primary or single most important purpose of the acquisition is tax avoidance or evasion, tax benefits are barred. . . .” and relying on speech in a corporate proxy statement as evidence).

⁷¹ 30 U.S.C. § 22 (2012) (“Except as otherwise provided, all valuable mineral deposits in lands belonging to the United States . . . shall be free and open to exploration and purchase . . . by citizens of the United States and those who have declared their intention to become such. . . .”).

⁷² *United States v. Bagwell*, 961 F.2d 1450, 1455 (9th Cir. 1992); see also *United States v. Langley*, 587 F. Supp. 1258, 1261 (E.D. Cal. 1984).

⁷³ 11 U.S.C. § 523(a)(6) (2016).

⁷⁴ *In re Kane*, 755 F.3d 1285, 1293 (11th Cir. 2014), cert. denied sub nom. *Kane v. Stewart Tilghman Fox & Bianchi, P.A.*, 135 S. Ct. 718 (2014).

speech, including an admission on the stand at trial, is excellent evidence of such intent.⁷⁵

Immigration law is rife with intent-based tests that transform otherwise legal behavior. For example, some visas require that the applicant have nonimmigrant intent.⁷⁶ If someone applies for a visa expressing a business purpose to travel to Ohio to purchase clothing for an export business, but then tells someone that he actually intends to go to North Carolina to live in a Subway restaurant (where he then will work illegally), those words may be used against him to show a fraudulent intent.⁷⁷

Most generally, conspiracy law depends on proof of an illegal intent and not much else (though there are technical distinctions between the general conspiracy and the drug conspiracy crimes).⁷⁸ It is not uncommon to use the conspirator's own speech to prove illegal intent.⁷⁹

Although the recitation may be tedious, we have seen intent-based tests in every area of the law studied. And, we have found the routine use of speech as evidence of intent. This form of regulation is ubiquitous apparently because it works so well to protect a general liberty for people to behave however they like, as long as they do not

⁷⁵ *Id.* at 1294 (affirming the non-dischargeability of a debt relying on debtor's admission at trial).

⁷⁶ 18 U.S.C. § 1546 (2012).

⁷⁷ *United States v. Khalaf*, 390 F. App'x 216 (4th Cir. 2010) (the Subway case).

⁷⁸ *United States v. Hardy*, 730 F. Supp. 1141, 1142-43 (D.D.C. 1990) ("The offense of conspiracy, as set forth in the general conspiracy statute, 18 U.S.C. § 371, is a specific intent crime. '[T]he specific intent required for [that offense] is . . . the intent to advance the unlawful object of the conspiracy.'" distinguishing the drug conspiracy crime, 21 U.S.C. § 846 as a general intent crime).

⁷⁹ *See, e.g., United States v. Rahman*, 189 F.3d 88 (2d Cir. 1999) (government used anti-US speeches and writings of Islamic cleric as evidence in criminal conspiracy case); *United States v. Tobin*, 480 F.3d 53 (1st Cir. 2007) (statements made by co-conspirator in harassment case used as evidence against defendant).

do so with an illicit intent. The behaviors with illicit intent are targeted, because those are the ones that impinge on larger policy interests (e.g., preventing money laundering or the distribution of guns to criminals).

For First Amendment theorists, this ubiquitous phenomenon exists on the margins. As Robert Post has written in other domains, “It is not that regulation of this conduct is affirmatively permitted by the First Amendment; it is rather that courts do not even subject such regulation to First Amendment scrutiny.”⁸⁰ Martin Redish has argued that FDA restrictions on commercial speech are incoherent when viewed from the political theory that justifies the First Amendment in the first place.⁸¹ We have here identified a different sort of coherence, cutting across many legal domains that use speech as evidence of criminal intent. That deep coherence is not necessarily a justification, but it does make the FDCA seem a bit less odd and a bit less worrisome.⁸²

CONCLUSION

In this short symposium paper, we have not solved the problem of off-label promotion or offered a new theory of the First Amendment. We have, however, shown how the FDA’s premarket approval process solves a collective action problem for new indications of approved drugs. Regardless of whether a company

⁸⁰ Robert C. Post, *Reconciling Theory and Doctrine in First Amendment Jurisprudence*, 88 CAL. L. REV. 2353, 2363-64 (2000) (While the *Spence* test holds that the First Amendment applies whenever there is an “intent to convey a particularized message,” in practice courts do not always apply the First Amendment to speech that passes that test.).

⁸¹ MARTIN REDISH, *THE ADVERSARY FIRST AMENDMENT: FREE EXPRESSION AND THE FOUNDATIONS OF AMERICAN DEMOCRACY* 65, 115 (2013) (criticizing logically indefensible distinctions).

⁸² See EPSTEIN, *supra* note 31 at 441 (“It hardly answers the challenge of these major economic impediments to say that they impose only an ‘incidental’ burden on the freedom of speech.”).

succeeds in securing a new labeled indication, the regulatory process produces and disseminates new information about the safety and efficacy of new intended uses. We have also shown that the FDA's intent-based test, and its use of speech as evidence of intent, are not at all peculiar. The law relies on this sort of regulatory mechanism ubiquitously to target its enforcement of behaviors that are most worrisome, while preserving a broader liberty. For innovation policy in particular, this mechanism tailors incentives to solve collective action problems and thereby produce knowledge about the chemicals that we put into our bodies.