



# Adding Shades of Gray to Black and White: Proposal for a Tiered Pharmaceutical Labeling Scheme

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# **Adding Shades of Gray to Black and White: Proposal for a Tiered Pharmaceutical Labeling Scheme**

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## **Abstract**

In the United States, \$26-54 billions are spent every year on the marketing of pharmaceuticals.<sup>1</sup> This article focuses on the scope and pros and cons of off-label use and marketing of pharmaceuticals, and proposes a new FDA regulatory structure to redirect the incentives to positives uses of off-label pharmaceuticals. The policy concern is to encourage research, treatment, and innovation, without allowing pharmaceutical companies to leverage the exclusivity that FDA approval brings for unwarranted sales that put patients at risk. The present legal regime encourages the FDA and pharmaceutical companies into Prisoner's Dilemma, where companies have every reason to attempt to use marketing to end run the agency, and the agency has every incentive institutionally to issue regulations which does not effectively address the problem. The losers, however, are those afflicted with conditions whose treatment would be improved by medications that are presently not indicated for their population, and patients who are prescribed medications which have neutral to adverse outcomes. By expanding the tiers of labeling to encompass standard of care, experimental, and orphan uses, companies will have greater incentive to pursue research which solidly shows that particular products are beneficiary treatments for a wider range of target populations.

## **Introduction**

In the United States, billions are spent every year on the marketing of pharmaceuticals; estimates in 2008 ranged from \$26 billion to \$54 billion US Dollars. Larger estimates include research which is done expressly for marketing purposes, as much as \$30 billion dollars, as well

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<sup>1</sup> Marc-André Gagnon & Joel Lexchin, *The Cost of Pushing Pills: A New Estimate of Pharmaceutical Promotion Expenditures in the United State*, 5 PLOS Med 29, 29–32 (2008).

as the distribution of samples, creation of marketing materials, meeting and talks sponsored for marketing, and purchase of advertising.<sup>2</sup> Of this research, the bulk is for marketed pharmaceuticals, in what is called Phase IV “seeding” studies, which by design is to promote the use of new drug rather than to obtain clinical data.<sup>3</sup> Battles between the Food and Drug Administration and pharmaceutical marketers, however, extend into virtually every form of marketing, including physician compensation, direct to consumer advertising (DTC) and now social media.

Since *Washington Legal Foundation v. Friedman*,<sup>4</sup> a period of unsettled attempts to regulate, clarify, and codify the marketing of pharmaceuticals in the United States has left the state of the law confused and treacherous.<sup>5</sup> On one hand, even the industry recognized that many of its marketing practices, including junkets to high prescribing physicians and physician profiling, were damaging to its own reputation, which is evidenced by the Pharmaceutical industries trade association, PhRMA, issuing a series of voluntary codes taken effect January 2009.<sup>6</sup> On the other hand, courts have been consistent in affirming that the tests outlined in *Central Hudson* are controlling for determining the scope of government’s power in restricting the commercial speech associated with FDA regulations.<sup>7</sup> The repeated attempts to introduce

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<sup>2</sup> *Id.*

<sup>3</sup> *Id.*

<sup>4</sup> *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d. 51 (D.D.C. 1998).

<sup>5</sup> See generally the proposals put forward by Joshua A. Weiss, *Medical Marketing in the United States: A Prescription for Reform*. 79 Geo. Wash. L. Rev., 260, (2010), <http://ssrn.com/abstract=1748902> and Mariestela Buhay, *Off-label Drug Promotion is Lost in Translation: a Prescription for a Public Health Approach to Regulating the Pharmaceutical Industry's Right to Market and Sell its Products*. 13 J. Health Care L. & Pol'y 459 (2010).

<sup>6</sup> PhRMA Code of Interaction with Healthcare Professionals, <http://www.phrma.org/about/principles-guidelines/code-interactions-healthcare-professionals>.

<sup>7</sup> Krista Hessler Carver, *A Global View of the First Amendment Constraints on FDA*, 63 Food & Drug L. J. 151 (2008).

FDA control over marketing of pharmaceuticals are at the most contentious when it comes to indications which are not part of the FDA approved label. This label details the range of uses which have been tested and examined by the FDA, and amount to the reason for granting the license to introduce the drug into inter-state commerce.

This article focuses on why the present legal regime for labeled drug marketing is ripe for change, requiring action from Congress. Presently, the issue tends to be framed in terms of commercial speech, which, because of the First Amendment freedom of speech, and federalism delegation to state regulation, creates a strong presumption routed in the governing cases in favor of companies being able to market any information which is available. Instead, the correct frame should be on the quality of information itself, and the overall public interest involved and the legal frame should be based on regulation of interstate commerce, which creates both a presumption of Federal supremacy, and basic constitutional authority. By creating a labeling system which moves the incentive of research away from creating marketing driven information, and towards scientific investigation and innovation, the aims and legitimate interests of the public can be better served, by moving enforcement from being aimed at regulations centered on marketing, to being centered on the license which the FDA grants to engage in interstate commerce, and the expectations that companies, doctors, and the public have of that license, it moves the legal question from whether companies have the right to speak, publish, or disseminate information, and to whether that information advances the public interest as embodied in the license.

The first part of this article focuses on the scope of off-label use and marketing of pharmaceuticals, and outlines the "baby and bath water" problem that policy faces. On one hand,

off-label uses of drugs are broadly useful, and frequently, the standard of care for particular illnesses, expanding the public good by increasing treatment options. Many drugs are not tested on broad patient populations, such as children. On the other hand, a large fraction of off-label prescriptions have little to no provable benefit, sometimes are medically harmful, and cost the public when better and less expensive treatments are available. There is ample evidence that marketing, rather than research, drives up costs and leads to medications that can endanger the public health. The policy concern is to encourage research, treatment, and innovation, without allowing pharmaceutical companies to leverage the exclusivity that FDA approval brings for unwarranted sales that put patients at risk, and to do so in a manner which will allow interests to be fairly treated in the legal system, while surviving legal scrutiny.

The second part of this article covers the present law, both in the application of the *Central Hudson* test, and in the variety of causes of action that have grown up to restrain inappropriate off-label marketing, as well as the complexity between labels to actual use. It shows that the present legal regime encourages the FDA and pharmaceutical companies into a less than optimal Prisoner's Dilemma, where companies have every reason to attempt to use marketing to end run the agency, and the agency has every incentive institutionally to issue regulations which strike at the leaves and branches of policy problems, without effectively getting to the roots of marketing losses.

The third part of the article outlines why more calibrated gradation of labeling serves policy interests and deals with legal issues most effectively. By expanding the tiers of labeling to encompass standard of care, experimental, and orphan uses, companies will have greater incentive to pursue research which solidly shows that particular products are safe and effective

treatments for a wider range of target populations. The enforcement of this new regime will be backed by sticks, in addition to carrots, with the FDA being able to use a powerful and credible set of sanctions against companies that do not adhere to the spirit of the labeling system.

The benefits to wider use of pharmaceuticals, in lowering costs, preventing trauma, extending and improving life are well understood. The high profile failures of the system have shaken public confidence, and created a standing opposition to pharmaceutical industry practices which unduly undermines the strength of the system. What is needed is a system which is better aligned with the realities of medical practice to preserve the beneficial off-label uses, promote R&D incentives to uncover useful clinical information, and reduce promotional behavior that poses public health threat and adds unnecessary costs to the healthcare system.

## ***Off Label Marketing Realities***

### **Marketing of Pharmaceuticals**

The industry practice of marketing of pharmaceuticals is not well documented in scholarly sources, and much of what is written is clearly from the perspective of advocacy for professionals, rather than objective descriptions of the institutional structures of marketing, or from the public health perspective, which, while it is often less overtly partisan, has a specific viewpoint and provenance as well, in that it seeks to advocate in an adversarial way for the interests of patients, or the public interest as being necessarily antagonistic to the industry. Internally pharmaceutical centers around access to gatekeepers: the physicians who write scripts, the insurance companies who approve payment, and the pharmacists who make recommendations to those seeking advice. The allocation of marketing dollars is overwhelmingly

on visits to physicians, and in particular the distribution of samples.<sup>8</sup>

Earlier in the decade the industry's main players recognized that marketing by incentives, which could include all expense paid trips to “conferences” which doubled as vacations, high speaking fees, and gifts unrelated to the practice of medicine were both bringing enough negative publicity to create moves to regulate the process, and casting doubt on the objectivity of the process. The sense in the industry is that such efforts were effectively canceling each other out. That is, the strategy of incentive had reached being a Prisoner's Dilemma, and that cooperation would be more effective. That there had been several high profile problematic attempts at creating a blockbuster through such marketing aided the industry's sense of crisis: Vioxx cast a long shadow. The industry's trade group, PhRMA, was the channel to promulgate guidelines on marketing, which ended the practice of such perks in marketing. What this means is that the increasingly adversarial relationship between how medications were approved, and how they were marketed, had produced a series of high profile failures, both on the public and private sides, and it had begun to be clear that the interest in unlimited marketing was being under-cut by the FDA becoming more conservative in approvals.

#### *Current Regulatory Scheme*

Currently, medical marketing is regulated by Division of Drug Marketing, Advertising, and Communications (DDMAC) as part of the Center for Drug Evaluation and Research (CDER) within the FDA. DDMAC is responsible for ensuring that prescription drug advertising and promotions does not out-step the approved label with information that is “false or

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<sup>8</sup> Marc-André Gagnon & Joel Lexchin, *The Cost of Pushing Pills: A New Estimate of Pharmaceutical Promotion Expenditures in the United State*, 5 PLOS Med 29, 30 (2008). (Table 1)

misleading.”<sup>9</sup> The bulk of DDMAC’s regulatory activities consist of reviewing and providing written comments on proposed promotional materials, monitoring promotional activities at medical meetings, investigating complaints about alleged violations and initiating enforcement actions, usually in the form of warning letters and corrective advertisements.<sup>10</sup> Stronger actions against promotional violations due to off-labeling marketing, such as large sum fines, are usually handled by the DOJ in form of civil and criminal litigation, though the FDA does have the authority to bring criminal sanctions against the CEO of companies that engaged in deviate promotional practices, a seldom-used, but powerful, deterrent, which the Agency employed in *Park* brought about by then General Counsel Peter Barton Hutt.<sup>11</sup>

FDA’s enforcement activity against off-label marketing, predominately through DDMAC, lacks specificity, prioritization, and sufficient resources to both monitor the landscape and go after the violators. A July 2008 report from the Government Accountability Office (GAO) concluded that FDA regulation of off-label pharmaceutical promotion has several significant regulatory limitations. First, the FDA regulates off-label marketing as part of a broader effort that targets many promotional violations, lacking a separate and targeted oversight mechanism. Second, the agency is overwhelmed by the volume of promotional materials submitted for review and has to prioritize based on the inherent public health threat, which the report proceeded to conclude is done in a un-systemic and unscientific manner. The FDA “relies on its staff to sort through large volumes of material and select submissions for review... is also hampered by the lack of a system that consistently tracks the receipt and review of submitted

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<sup>9</sup> DDMAC mission on FDA website, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/DrugMarketingAdvertisingandCommunications/ucm209384.htm#DDMACsMission>.

<sup>10</sup> *Id.*

<sup>11</sup> *Park v. United States*, 421 U.S. 658 (1975).

materials.”<sup>12</sup> The numbers tell a similar story of strained resources and delayed enforcement. FDA took an average of 7 months to issue warning letters, followed by another 4 months for corrective action by drug companies with more serious offenses. Between 2003 and 2007, FDA referred no violation to the Department of Justice (DOJ) for further enforcement action. Meanwhile, the DOJ has pursued litigation that resulted in 11 settlements all identified by sources other than the FDA.<sup>13</sup>

Not only is the institutional structure and the regulatory scheme insufficient, but also there is the enforcement loophole that the medical entities with a pharmaceutical company (e.g., the departments overseen by the Chief Medical Officer (CMO)) are not subject to the same stringent promotional standards as the sales divisions, because CMOs and other medical officers are supposedly interfacing with the practice of medicine, of which outside the FDA’s regulatory authority both by statute and case law. Because the medical officer is a licensed physician, the ethical guidelines reconciles with the long-standing practice of allowing physicians to freely prescribe drugs for off-label uses<sup>14</sup> and to influence the prescribing habits of their fellow physicians, as in the practice of “Key Opinion Leaders” or KOLs. It is industry common practice to leave some of the “gray area” promotional activity to the medical divisions, which handle journal reprint distribution and continue medical education. According to an industry source, a major pharmaceutical company tasked a portion of its sales force as liaisons between physicians and the medical divisions, which then promotes the unapproved uses liberally through journal reprints. The medical divisions also actively cultivate “Key Opinion Leaders,” or KOLs, who are

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<sup>12</sup> GAO, *Prescription Drugs: FDA’s Oversight Of The Promotion Of Drugs For Off-Label Uses*. Report to the Ranking Member, Committee on Finance, U.S. Senate (July 2008).

<sup>13</sup> *Id.*

<sup>14</sup> Michelle M. Mello et al., *Shifting Terrain in the Regulation of Off-Label Promotion of Pharmaceuticals*, 360 *New Eng J Med*. 1557, 1557–66 (2009).

allowed to educate other physicians on the off-label uses with little limitation, under the façade of practice of medicine. Because FDA is strictly prohibited from regulating the practice of medicine, industry end-runs the Agency's enforcement efforts by using doctors to persuade doctors.

The policy question of off-label prescribing requires balancing both the benefits and the risks of these prescriptions in the practice of medicine. The practice is wide spread: one commonly cited estimate is that 21% of all prescriptions are off-label.<sup>15</sup> Federal law explicitly authorizes off-label prescriptions for approved drugs,<sup>16</sup> and even compensates them under Medicaid and Medicare.

However, not all off-label is created equal. The highly prevalent practice differs greatly on its medical justifiability and potential for harm. For example, the American Cancer Society found that 80% of all oncologists had written an off-label prescription.<sup>17</sup> Patients facing terminal disease have far less to risk than others, and the survey evidence indicates that physicians are far more willing to prescribe off-label use.

While some off-label use of chemotherapy drugs should be encouraged because the innovation outpaces FDA approval and these drugs can be lifesaving for rare cancers, negative clinical trials results often demonstrate the lack of benefit or even harm of off-label use.<sup>18</sup> In pediatrics, because drugs are generally approved for adult populations and the drug companies

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<sup>15</sup> David C. Radley et al., *Off-label Prescribing Among Office-Based Physicians*, 166 *Archives of Internal Med.* 1021, 1025 (2006).

<sup>16</sup> Food and Drug Modernization Act § 214, 21 USC § 396 (1997).

<sup>17</sup> American Cancer Society, What is off-label drug use?  
<http://www.cancer.org/Treatment/TreatmentsandSideEffects/TreatmentTypes/Chemotherapy/off-label-drug-use>.

<sup>18</sup> Frederic R. Curtiss & Kathleen A. Fairman. *Contradictory Actions on Off-Label Use of Prescription Drugs? The FDA and CMS Versus the U.S. Justice Department*. 15 *J. Managed Care Pharmacy* 161, 163 (2009).

are often reluctant to invest in trials involving pediatric population, except at the end of the exclusivity period to gain the six-month extension of market exclusivity giving to pediatric indications, there is often no approved drug at all in a particular category. In 1996 one study, found that 81% of HIV patients received at least one off-label prescription.<sup>19</sup> Off-label can also mean that the route of delivery is not FDA approved, for example taken orally if the medication was approved for injection.

Alexander T. Tabarrok summarized the prevalence of off-label in a medical practice:<sup>20</sup> “In summary, off-label prescribing is common in every field of medicine, and in a large number of fields most patients are prescribed at least one drug off-label. It is clear that if the FDA were to attempt to prohibit doctors from prescribing off-label, current practices would have to change significantly.” He then cites a celebrated example of beneficial off-label use:

In 1982, Barry Marshall and Robin Warren discovered in the stomachs of ulcer sufferers a new bacterium, *Helicobacter pylori*, which they hypothesized was the cause of the ulcer. Their theory was initially highly controversial, but it is now believed that most stomach ulcers (perhaps 90 percent or more) are caused by *Helicobacter Pylori*. Using antibiotics such as amoxicillin and tetracycline, these ulcers can now be cured. Although hundreds of thousands of prescriptions have been written to this effect, all have been off-label. Neither amoxicillin nor tetracycline is approved for use in the treatment of stomach ulcers.<sup>21</sup>

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<sup>19</sup> Carol L. Brosgart, *Off-Label Drug Use in Human Immunodeficiency Virus Disease*, 12 J. Acquired Immune Deficiency Syndromes & Hum. Retrovirology 56, 56 (1996).

<sup>20</sup> Alexander T. Tabarrok, *Assessing the FDA via the Anomaly of Off-Label Drug Prescribing*, 1 The Independent Rev. 25, 46 (2000).

<sup>21</sup> *Id.* at 27.

The risks of off-label use are equally important to consider. According to Hazel Muir study, 71% of all off-label prescriptions were useless or harmful.<sup>22</sup> Jacob Rogers in "Freedom of Speech and the FDA's Regulation of Off-Label Drug Uses" cites the "fen-phen" prescriptions, which caused heart valve damage to 285,000 patients, and Roberts regards this as a conservative estimate.<sup>23</sup> In the area of psychiatry and pain management, companies have frequently promoted atypical antipsychotics or scheduled painkillers off-label broadly without supporting medical evidence of efficacy or safety. "As part of its comparative effectiveness research, AHRQ concluded in 2007 that there was 'insufficient high-grade evidence to reach conclusions about the efficacy' of atypical antipsychotics (e.g., olanzapine, quetiapine, risperidone, ziprasidone) for off-label uses such as dementia, severe geriatric agitation, depression, obsessive-compulsive disorder, autism, Tourette syndrome, post-traumatic stress disorder, and personality disorders."<sup>24</sup> Another example of the anticonvulsant Neurontin (compound name: Gabapentin), originally indicated for epilepsy, a limited growth market with relatively small patient population, expanded to having as much as 90% of its prescriptions off-label for a wide variety of indications,<sup>25</sup> Its journey to a blockbuster is often cited as a successful story within the pharmaceutical industry and widely enumerated. In pain management, the severe consequences of off-label use of certain strong opioids, such as Actiq and Fentora, have resulted in the FDA to consider imposing an Approved Risk Evaluation and Mitigation Strategies (REMS) program on

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<sup>22</sup> Hazel Muir, *Dicing with Death: There's a Good Chance that the Pills Your Doctor Prescribed Will Do You No Good and Might Even Harm You*, *New Scientist*, 38, 40 (2006).

<sup>23</sup> Jacob Rogers, *Freedom of Speech and the FDA's Regulation of Off-Label Drug Uses*, 76 *Geo. Wash. L. Rev.*, 1429, 1433 (2008).

<sup>24</sup> Frederic R. Curtiss & Kathleen A. Fairman. *Contradictory Actions on Off-Label Use of Prescription Drugs? The FDA and CMS Versus the U.S. Justice Department*. 15 *J. Managed Care Pharmacy* 161, 163 (2009).

<sup>25</sup> Jacob Rogers, *Freedom of Speech and the FDA's Regulation of Off-Label Drug Uses*, 76 *Geo. Wash. L. Rev.*, 1429, 1433 (2008).

the entire Opioid Class,<sup>26</sup> and the approval of Onsolis, for breakthrough cancer pain, in July 2009 under REMS.<sup>27</sup>

Nevertheless, some off-label uses are often supported by medical literature, or by clinical practice. FDA can and should encourage the dissemination of information about off-label uses in the high-benefit situations, while discouraging and informing physicians and patients when its efficacy or safety is in question. However, current regulatory scheme does not afford the FDA such a high degree of flexibility. The prescription drug labeling process is, by intent and design, narrow and rigorous, and becoming increasing so in the post-Vioxx world. This means that it is also expensive and time consuming to get indications approved for the label. Therefore, once a drug is on the market, even more so after genericization, there is far less economic incentive to pursue widening the label, particularly since the provision of the Budget Reconciliation Act of 1993 mandated that insurance companies and Medicaid reimburse for medically sound off-label uses.<sup>28</sup> The ideal policy would work to increase economic incentives to encourage testing and collection of information before and during the market exclusivity period before generic entry.

One problem in off-labeling marketing is there is clear evidence that pharmaceutical companies have attempted to influence medical information at the source. The altering and obscuring of data with respect to drugs has a long and tangled history, most notably in the case of Vioxx, where it was found that Merck systematically used ghostwriters and guest authorship to

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<sup>26</sup> *American Pain Foundation Endorses Opioid Class REMS Recommendations to FDA: Consensus Recommendations*, Developed by the Pain Care Forum REMS Task Force (June 2009), <http://www.painfoundation.org/about/position-statements/rem-recommendations.pdf>.

<sup>27</sup> *FDA Approves Opioid Pain Reliever with Required Risk Reduction Plan*, FDA New Release, (July 16, 2009),

<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm172366.htm>.

<sup>28</sup> Omnibus Budget Reconciliation Act, 42 U.S.C. §1395 (s)(2) (1993).

down play the death rate associated with the medication.<sup>29</sup> Of the 20 papers, 16 were originally drafted by a Merck employee or contractor, but were later listed as the work of an independent researcher.<sup>30</sup> The JAMA study concluded that Merck had been "less than candid" in its disclosures to FDA regarding heart attack risks.<sup>31</sup> The quality of the information stream, not the means of delivering it to the doctor's office, is of greater concern. Yet, there has been almost no focus from the agency on protecting the quality of the information at the source.

Nor is there any evidence that fines imposed by the DOJ, even some over a billion dollars, have had significant deterring effect. For example in September of 2009, Pfizer paid a total of \$2.3 billion US Dollars to settle off-label marketing claims for a drug that had already been removed from the market.<sup>32</sup> The fact that such fines have become routine in recent years indicates the incentives to broaden the use of a drug by marketing off-label is huge, because of the strong motives to create, or protect, a blockbuster drug and high competitive pressure to maximize returns on approved drugs before generic entry. According to the 2009 Med Ad Report on top prescription medications, the top 500 prescription medications generated \$423 billion US Dollars in sales, almost half of which came from the US.<sup>33</sup> The cost-benefit analysis falls differently from widening of label for a drug to approve for a new indication to one that is approved for one delivery route, but not others. The present labeling system does not offer a sufficient number of gradations to represent the different levels of risk and probable benefits, in

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<sup>29</sup> Ross et al., *Guest Authorship and Ghostwriting in Publications Related to Rofecoxib: Case Study*, 299 JAMA, 1800, 1800–12, (2008).

<sup>30</sup> *Id.*

<sup>31</sup> *Id.*

<sup>32</sup> David Evans, *Pfizer Broke the Law by Promoting Drugs for Unapproved Uses*, Bloomberg News (November 9, 2009), <http://www.bloomberg.com/apps/news?pid=newsarchive&sid=a4yV1nYxCGoA>

<sup>33</sup> Andrew Humphreys & Rebecca Mayer, *World's Best-Selling Medicines*, Med Ad News (2009), available at <http://pharmalive.com/magazines/medad/view.cfm?articleID=2129>.

essence placing a barrier to entry for indications that are the standard of care, while allowing end runs of the agency for prescriptions of dubious medical value, because to expand an indication, the license holder must prove a positive benefit, while to persuade physicians to expand prescribing, the FDA must prove that it is harmful, or does no good at all.

The very fact of physicians and other healthcare professionals relying solely on journal studies and anecdotal evidence, often collectively inclusive, points to a policy failure: because of the black or white nature of FDA labeling, there is no official government stream of data to follow. Evidenced based medicine requires evidence; the lack of data on which prescriptions were written for which purposes and their relationship to the current label make it difficult to judge the efficacy and dangers of courses of treatment in the target population.

In summary, in many cases, the requirements to prove efficacy to third-party payers, through prior authorization and other types of managed care are enough for physicians to choose effective off-label prescriptions, or at least those which, on balance, are possibly more beneficial than harmful. Even a prescription which might have worked is defensible in the case of terminal patients or those with highly negative expected outcomes. However, in other cases such as Vioxx, the pressure to create a blockbuster drug created incentives to abuse the peer review and government reporting systems, leading to a situation where a drug was prescribed well beyond the population which it could benefit, and as a result harming patients who stood nothing to gain from the particular treatment.

### **Beneficial Off-label Use: Pediatrics and Oncology**

It is widely accepted that pediatrics and oncology are two areas of medicine, which have

the most benefit from "off-label" use of medications. For example in the "Off-Label Use of Medical Products Position Statement" from the American Academy of Orthopedic Surgeons:

In certain patient populations, off-label use of medical products is extensive where appropriate therapies are not available. Two of those populations include oncology and pediatric patients. Oncology patients depending on the type and severity of the disease are frequent recipients of off-label therapies. The FDA has recently recognized the need for accelerating the approval of cancer drugs. Pediatric surgeons are likely to use off-label therapies on neonates, infants, children, and adolescents due to the lack of on-labeled medical products on the market. Surgeons find a lack of approved pediatric devices for many reasons including a historical exclusion of children in medical trials, and liability concerns among other issues. In 2007, the Congress recognized significant issues with pediatric device development and signed the Pediatric Medical Device Safety Act into law as part of the Food and Drug Administration Act Amendments of 2007.

This recognition is grounded in the nature of the approval process for drugs. According to "Off-Label Prescribing to Children in the United States Outpatient Setting" found:

Sixty-two percent of outpatient pediatric visits included off-label prescribing.

Approximately 96% of cardiovascular-renal, 86% of pain, 80% of gastrointestinal, and 67% of pulmonary and dermatologic medication prescriptions were off-label. Visits by children aged <6 years had a higher probability of off-label prescribing ( $P < .01$ ), especially visits by children aged <1 year (74% adjusted probability). Visits to specialists also involved a significantly increased probability (68% vs. 59% for general

pediatricians,  $P < .01$ ) of off-label prescribing.<sup>34</sup>

While the exact results of marketing are arguable, such percentages indicate that for pediatric care, the off-label drug is not merely a potential option, but for some conditions, the standard of care. On one hand, the United States has been considered to be ahead of Europe in expanding labeling to increase access to pediatric medications.<sup>35</sup> On the other hand, Europe has a more extensive literature of surveying pediatric practice, with many studies even in American Journals being compiled from clinical experiences in Germany, the Netherlands, or Europe as a whole. The result of more extensive studies can indicate a substantially increased patient risk:

Recently marketed products also pose safety concerns for children. For example, propofol, a sedative-hypnotic, was marketed in 1989 in the U.S. and used for pre-anesthesia induction. Trial data in children from 1988 showed it had a 9% mortality rate in critically ill patients with upper respiratory tract infections compared with 4% for standard sedatives, but causality was not established. Since then, propofol's use in pediatric intensive care units has been linked with 'propofol infusion syndrome'. This syndrome induces hypotension and metabolic acidosis, and produces a propofol metabolite that may induce toxicity or predispose patients to sepsis. In the summer of 2003, the FDA recommended a warning letter be sent to doctors based on adverse event reports from MedWatch (the FDA voluntary post-marketing surveillance reporting system). This experience illustrates that the original recommendations for dosage and rate

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<sup>34</sup> Alicia T.F. Bazzano et al., *Off-Label Prescribing to Children in the United States Outpatient Setting*, 9 *Acad. Pediatrics*, 81, 81 (2009).

<sup>35</sup> Eric Schirm et al., *Hospital Risk Factors for Unlicensed and Off-Label Drug Use in Children Outside the Hospital*, 111 *Pediatrics* 291, 294 (2003).

of administration were not appropriate for all neonates and that the drug's usage in clinical trials could not be generalized to longer exposures or more rapid rates of titration in neonates treated in the community.<sup>36</sup>

Clearly, the 6 month exclusivity period for a pediatric indication and trials requirement are addressing a very real problem that of not having rigorous clinical data on which to make evidence based decisions. However, data such as these shows that on one hand, it is virtually a necessity to prescribe off-label for broad classes of condition in pediatrics. On the other hand, the consequences of incorrect dosage in children can result in fatalities. None of this suggests any wrong doing on the part of any of the parties involved in the case of propofol, or in other similar specific cases outlined. The problem is purely one of information.

The possibility that marketing could be driving misuse of medications has been brought up in the case of Prilosec in infants. Prilosec is an anti-acid drug prescribed for adults with acid-reflux. However, in children, it is not acid that causes the majority of spit ups, according to Gremase in "GERD in the Pediatric Patient: Management Considerations":

These results suggest that in some individuals, GERD [Gastroesophageal reflux disease] is a lifelong disease that may require aggressive therapy early in life to reduce the risk of long-term sequelae, such as erosive esophagitis or Barrett's esophagus. Therefore, because GERD is common, it is important to distinguish pediatric patients with pathologic reflux that may lead to complications of GERD from those with physiologic GERD who have a better prognosis. The presence of associated symptoms such as poor

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<sup>36</sup> Julie M Zito et al., *Off-Label Psychopharmacologic Prescribing For Children: History Supports Close Clinical Monitoring*, 2 Child. & Adolescent Psychiatry & Mental Health 24, 24 (2008).

weight gain, excessive crying, disturbed sleep, and feeding or respiratory problems distinguishes infants with GERD from those with physiologic gastroesophageal reflux.<sup>37</sup>

While there is a population that needs intervention, most do not. According to Schwarz et al.:<sup>38</sup>

Although minor degrees of gastroesophageal reflux are noted in both children and adults, the degree and severity of reflux episodes are increased during infancy. Thus, gastroesophageal reflux represents a common physiological phenomenon in the first year of life. As many as 60-70% of infants experience emesis during at least one feeding per 24-hour period by age 3-4 months. The distinction between this "physiologic" gastroesophageal reflux and "pathologic" gastroesophageal reflux in infancy and childhood is determined, not merely by the number and severity of reflux episodes (when assessed by intraesophageal pH monitoring), but is most importantly determined by the presence of reflux-related complications, including failure to thrive, erosive esophagitis, esophageal stricture formation, and chronic respiratory disease.

To summarize: reflux, or spitting up or vomiting, is common in infants, while for some children it is the sign of the onset of a long-term condition, where acid and problems with GI function are the beginning of a long term pathology. However for the majority of children, it is not serious. Because of this, the standard of care from medical literature has been stable for

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<sup>37</sup> David A Gremse, *GERD in the Pediatric Patient: Management Considerations*, 6 MedGenMed 13 (2004), <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1395762/>.

<sup>38</sup> Steven M. Schwarz, *Pediatric Gastroesophageal Reflux*, Medscape Reference (January 13, 2010), <http://emedicine.medscape.com/article/930029-overview>.

sometime, suppressing the acid is far less important in children than dealing with the muscle problem, and conservative therapy should be used.<sup>39</sup> The same warning is repeated in 2004.<sup>40</sup>

However against these repeated warnings that GERD requires observation, that there are evidence based guidelines from the American Academy of Pediatrics<sup>41</sup> what has been observed in a clinical setting is the reverse:<sup>42</sup>

Only 8 of 44 pH studies showed abnormal acid reflux. Forty-two of these 44 infants were already on antireflux medications. Other etiologies included hypertrophic pyloric stenosis (4) and renal tubular acidosis (1). Discontinuation of medication did not result in worsening of symptoms in most infants with normal pH studies.

To summarize, less than 20% of the infants on anti-reflux medications met the clinical guidelines. However, when the medications were withdrawn, 6 of the 36 infants worsened in condition. This is not to draw cause and effect, but to show that even in the population that does not meet the current standard of care, medications—and all of these prescriptions were either OTC or off-label— may be of some benefit. The challenge is to produce a labeling system that will promote, not “the standard of care” but to promote the good of the patients.

GERD is merely one of thousands of conditions treated by hundreds of compounds in millions of pediatric care visits. From the forgoing it can be seen that simple Manichean divisions of "off-label" being good or bad are not supported by the peer reviewed evidence. Even

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<sup>39</sup> SR Orenstein et al., *Gastroesophageal Reflux Disease In Children*, 28 *Gastroenterology Clinics N. Am.*, 947, 947 (1999).

<sup>40</sup> Shawna M. Henry, *Discerning Differences: Gastroesophageal Reflux And Gastroesophageal Reflux Disease In Infants*. 4 *Advances Neonatal Care*, 235, 235–47 (2004).

<sup>41</sup> *Id.* at 235.

<sup>42</sup> Vikram Khoshoo et al. *Are We Overprescribing Antireflux Medications for Infants With Regurgitation?* 120 *Pediatrics* 946, 946–48 (2007).

when the standard of care does not recommend medication, sometimes it can be effective, but often it is harmful. There are no clear indications from the FDA, or from the compendia that physicians rely upon. Even where such guidelines exist, as they do in the case of GERD, they are routinely ignored, or not followed. The present labeling regime does not advance the public good or the benefit of a large population in the cases outlined. When virtually all medications in a target population are used off-label, then clearly there has been both market failure and regulatory failure. In a large number of identifiable populations it does not provide enough information for physicians, and is not available in a manner which allows for evidence based diagnosis in a clinical setting. The lack of granularity of information hinders good decisions from patients, doctors, industry participants, and regulators.

Since, in the end, the costs of these problems are born by the government, and the public in the form of health care and insurance costs, it is incumbent on the FDA, as the agency charged with protecting the public good in this area, and the Congress, charged with legislating where it is “necessary and proper,” to act on the evidence of regulatory failure which is pervasive in almost every area of medical practice. Since the particular areas where over-prescribing: pain management and psycho-actives, touch on every area of medical practice, and the areas where labeling is a hindrance: terminal patients are those of extreme urgency to the afflicted patients and their families, this is not a marginal defect in the law and its application.

### ***Problems with the Current Legal Regime***

The present legal regime of drug marketing faces a series of legal problems that make the already outlined policy problem more difficult. The first is the well understood First Amendment

problem and the repeated failure for both the Agency, and Congress, to draft regulations which can withstand the *Central Hudson* Test for the permissibility of government restraint on commercial speech. The second is the failure of mechanisms such as misbranding suits and the Fraudulent Claims Act based system to restrain off-label marketing abuses, and the defects with reliance on *qui tam* suits in the case of drug marketing. The third is the proliferation of jurisdictions that the first two problems have in no small part created. These three problems with the present legal regime argue for a more thorough revision of the means by which drug marketing is integrated into advancement of legitimate interest of the public.

In the final section of the paper, reasons for this dramatic drop in approvals will be explained in terms of the Prisoner's Dilemma, and solutions for a legislative process less prone to such a disconnect between stated goals and results will be sketched. The first is the failure of its drug marketing provisions to pass basic First Amendment tests, codified by the Supreme Court in what is known as the *Central Hudson* Test. The second is the failure of *qui tam* suits to be an adequate secondary mechanism in schemes to promote off-label marketing as an end run around the approval process, and the third is the welt of jurisdictions that a restraint and law suit based approach to enforcement has resulted in.

### ***Central Hudson and Prior Restraint Failures***

Before the FDAMA, Congress attempted to curb abuses in reselling of drugs with the Prescription Drug Marketing Act of 1987. It specifically forbade reselling of free samples, required distribution of samples only under regulated conditions, and permitted only

manufacturers the right to re-import their own drugs, except in emergencies.<sup>43</sup> Overall the PDMA, while effective in ending the particular abuses it was targeted to restrain, did not serve as a broad mandate for the agency to regulate or restrict marketing activities. The PDMA, however, has not been seriously challenged because it rests squarely on the Interstate Commerce Clause, and the ability of the Federal Government to regulate the introduction of goods into interstate commerce.

The attempts in the FDAMA and subsequent to regulate speech, as opposed to distribution, however, are not as firmly founded constitutionally. It is not that the FDAMA regime is universally anti-marketing, on the contrary, Direct to Consumer (DTC) marketing was allowed and expanded, but it is that attempts to create very narrow regulations on the manner of marketing unapproved, but potentially beneficial, practices failed to meet *Central Hudson* Test.

In *Central Hudson Gas & Electric Corp. v. Public Service Commission*,<sup>44</sup> Powell's opinion created a four part standard for government banning of commercial speech:

1. Is the speech protected? That is it must be lawful, and not be fraudulent or misleading?
2. Does the government assert a "substantial" interest?
3. Does the regulation "directly" advance the government interest asserted?
4. Is the regulation the least intrusive way of advancing the government's asserted interest?

This four part test creates three hurdles for government regulation of speech. The court is allowed to judge the motivation of the government action, its efficiency in performing advancing the interest, and means by which it does so, including alternative means. There is little evidence

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<sup>43</sup> Prescription Drug Marketing Act (PDMA), Pub. L. No. 100-293, §§203.30–34, 102 Stat. 95 (1987).

<sup>44</sup> *Central Hudson Gas & Elec. Corp. v. Public Service Commission*, 447 U.S. 557 (1980).

that this standard is due to be relaxed, in fact, in *44 Liquormart, Inc. v. Rhode Island*<sup>45</sup> showed that the court believed that regulations on advertising were suspect even before *Central Hudson*, by citing the older *Virginia Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, where a state blanket ban on advertising prices was overturned.<sup>46</sup> The court affirmed that while the fourth part does not need to be perfect, it must be "reasonable," that is reasonably close to the least intrusive way of achieving a substantial interest directly. In *44 Liquormart*, the court approvingly quoted Brandeis' famous dictum from *Whitney v. California*: "the remedy to be applied is more speech, not enforced silence. Only an emergency can justify repression."<sup>47</sup>

Therefore, it is not difficult to see why in two separate cases, courts overturned the FDAMA on this exact point. The first time was in *Washington Legal Foundation v. Friedman*,<sup>48</sup> and then again in *Western States Medical Center v. Henney*.<sup>49</sup> In the first case off-label marketing restrictions were overturned, and in the second the restrictions on pharmacists marketing particular compounded drugs without needing to go through a separate FDA approval was struck down. Despite this background the agency continues to issue guidelines and make statements which seem to hinge on submission and pre-approval of marketing materials.

## **False Claims Act**

The Federal False Claims Act (FCA) 31 U.S.C. §§ 3729-3733 imposes triple damage liability on a party who knowingly submits false records to the federal government in hopes of

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<sup>45</sup> *44 Liquormart, Inc. v. Rhode Island*, 517 U.S. 484 (1996).

<sup>46</sup> *Virginia Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc.* 425 U.S. 748 (1976).

<sup>47</sup> *44 Liquormart*, 517 U.S. 484.

<sup>48</sup> *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d. 51 (D.D.C. 1998).

<sup>49</sup> *W. States Med. Ctr. v. Henney*, 202 F.3d 331, 333–34 (D.C. Cir. 2000).

payment, such as Medicare/Medicaid receipts.<sup>50</sup> Originally passed in 1863, the FCA was spurred by cases of fraudulent goods sold to the Union war effort, including suits *qui tam pro domino rege quam pro se ipso in hac parte sequitur*, which translates to “who pursues this action on our Lord the King's behalf as well as his own,” or “*qui tam*” for short.<sup>51</sup>

The *qui tam* cause of action allows a private plaintiff, who knows of a fraud against the government, to initiate a lawsuit on behalf of the government, in return for a share of the proceedings if successful.<sup>52</sup> In the context of off-labeling marketing, whistleblowers help the United States government seek recovery for claims paid by government health programs resulting from these unapproved marketing practices. In turn, the private plaintiffs, known as "relators," are entitled to 15% to 30% of the government's recovery, plus legal fees and other related costs.<sup>53</sup> Companies can be, and have been, sued both by the government and by *qui tam* whistleblowers.<sup>54</sup>

The FCA creates a tension between the ability of the law to generate “private Attorneys Generals” to assist the government in preventing fraud with their insider knowledge and the creation of suits regarded as opportunistic, trying to reap rewards over false accusations or without providing information that is helpful for the prosecution.<sup>55</sup> As a matter of fact, Congress has amended the act several times to “walk a fine line between encouraging whistle-blowing and discouraging opportunistic behavior,” which resulted in a series of subject matter jurisdictional

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<sup>50</sup> Shelley R. Slade, *Off-Label Promotions Pursued under the False Claims Act*, (September 2007) <http://www.false-claims-act-health-care-fraud-whistleblower-attorney.com/articles/off-label-promotions.php>.

<sup>51</sup> *United States ex rel. Duxbury v. Ortho Biotech Prods., L.P.*, 579 F.3d 13, 16 (1st Cir. 2009).

<sup>52</sup> Robert Vogel, 2009 Amendments to False Claims Act, (2009) [http://www.false-claims-act-health-care-fraud-whistleblower-attorney.com/articles/2009\\_Amendments\\_FCA.php#](http://www.false-claims-act-health-care-fraud-whistleblower-attorney.com/articles/2009_Amendments_FCA.php#).

<sup>53</sup> *Hopper v. Solvay Pharms., Inc.*, 588 F.3d 1318, 1324 (11th Cir. 2009).

<sup>54</sup> *Id* at 1322.

<sup>55</sup> 579 F.3d at 16.

bars that relators must satisfy in order to bring *qui tam* cases in federal court.<sup>56</sup>

The FCA has been used as one of the primary weapons in enforcing drug marketing regulations, especially in recent years, as evidenced by the large DOJ settlements.<sup>57</sup> Since the federal government doesn't regulate the practice of medicine and leaves the use of drugs to the judgment of physicians (state law regulates the practice of medicine through medical licensure and malpractice tort law), the Federal Government specifically contemplates off-label use of FDA-approved drugs and compensates physicians for off-label prescriptions. Therefore, it is legal for a company to submit claims to federal healthcare programs that have not been FDA-approved. However, it is illegal for a pharmaceutical company to engage in organized marketing of off-label claims that persuade physicians to write prescriptions for off-label uses.<sup>58</sup>

Government programs generally will cover drugs only if their use is "reasonable and necessary" in a "safe and effective" manner, as determined by FDA approval or citation in medical compendia. The submission of a claim otherwise is a false claim, and if it is due to off-label marketing, the pharmaceutical company is considered to have provided causation, by kicking off the chain of events that led to the submission of the false claims to the government. The FCA is more commonly used, however, by whistle-blowers with insider information, who are often employed by the pharmaceutical industry, directly against hospitals and doctors, engaging in more prosaic billing schemes for services not rendered, or drugs not actually dispensed.

The FCA has been applied to Medicare and Medicaid billing with the Deficit Reduction

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<sup>56</sup> *Id.*

<sup>57</sup> Edward P. Lansdale, *Used as Directed - How Prosecutors Are Expanding the False Claims Act to Police Pharmaceutical Off-Label Marketing*, 41 New Eng. L. Rev. 159 (2006-2007); Peter B Hutt et al. Food and Drug Law, 555 (2007).

<sup>58</sup> Peter B Hutt et al. Food and Drug Law, 548, 554-55. (2007).

Act of 2005 ( DRA),<sup>59</sup> including the attempt to submit billings for off-label marketing which falls outside of permitted FDA regulations. However, high profile cases, including Pfizer's Bextra which concluded with \$2.3 billion settlement with DOJ, and Eli Lilly's Zyprexa for \$1.415 billion, were not *qui tam* suits.<sup>60</sup> Because relators must not only know of the scheme to engage in off-label marketing, but must have personal knowledge of payments, or show that false claims were paid, their ability to successfully make a claim in complex off-label marketing schemes is limited, as shown by the 2009 11<sup>th</sup> Circuit decision of *Hopper v. Solvay*.<sup>61</sup>

We will assume *arguendo* that when a physician writes an off-label prescription with knowledge or intent that the cost of filling that prescription will be borne by the federal government, and when a claim is ultimately submitted to the federal government to pay for that prescription, 31 U.S.C. § 3729(a)(1) may have been violated....Nonetheless, the relators' Complaint does not identify a single physician who wrote a prescription with such knowledge, does not identify a single pharmacist who filled such a prescription, and does not identify a single state healthcare program that submitted a claim for reimbursement to the federal government. The relators contend that their Complaint "contains factual allegations which reliably indicate that false claims were submitted to the Government." We disagree. The Complaint piles inference upon inference to suggest that Solvay's marketing campaign influenced some unknown third

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<sup>59</sup> Deficit Reduction Act of 2005, Pub. L. No. 109–71, §6031, 120 Stat. 4, enacted February 8, 2006.

<sup>60</sup> See Department of Justice, *Eli Lilly and Company Agrees to Pay \$1.415 billion to Resolve Allegations of Off-label Promotion of Zyprexa*, (January 15, 2009), <http://www.stopmedicarefraud.gov/pfizerfactsheet.html> (DOJ found that there were 11 overlapping suits in the case of Bextra, but it was the criminal case which forced the plea and resolution).

<sup>61</sup> 588 F.3d at 1324, 1326.

parties to file false claims. We cannot conclude that the Complaint satisfies the particularity requirements of Rule 9(b)...

In *Solvay*, the U.S. Court of Appeals for the Eleventh Circuit ruled that the complaint of the relator is deficient under the heightened pleading standard of Federal Rules of Civil Procedure 9(b) that the party must “state with particularity the circumstances constituting fraud or mistake.”<sup>62</sup> In the context of the FCA, this means the relator must be able to make specific factual allegations that identify the physicians, pharmacists, or health programs that were involved. The Court also made a less relator-friendly interpretation of the Act, adopting an interpretation of the FCA that leads to a more stringent pleading standard on both parts of the FCA, making it more difficult for private plaintiffs to successfully bring suit. In 31 U.S.C.S. § 3729(a)(1), there is a “presentment clause” that imposes liability on any person who “knowingly presents, or causes to be presented, to an officer or employee of the United States Government...a false or fraudulent claim for payment or approval.”<sup>63</sup> The 11th Circuit, on public policy grounds, required indication of an actual false claim with specific factual allegations to satisfy the heightened pleading standard of Rule 9(b).<sup>64</sup> While §3729(a)(2) does not have a presentment requirement, the court, nevertheless, held that relators must show that the government paid a false claim to prove a violation of FCA. The rationale is that it is congressional intent to impose liability only when the false statements actually cause the government to pay amounts it does not owe.<sup>65</sup>

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<sup>62</sup> *Id* at 1324.

<sup>63</sup> 31 U.S.C.S. §3729(a)(1).

<sup>64</sup> 588 F.3d at 1325.

<sup>65</sup> *Id* at 1328.

This decision is a severe blow to the use of the FCA by private relators in enforcement of off-label marketing rules, because now they must have specific evidence—not merely an attempt to engage in off-label marketing, but an account of who wrote such prescriptions. Since most personal medical data is protected by HIPAA, relator claims under the FCA will likely be unsuccessful, absent monumentally obvious behavior or continued efforts to defraud the government through inducement of off-label prescription writing despite concerted investigation.

Further adding to the uncertainty is *United States ex rel Duxbury v. Ortho Biotech Products*, decided by the First Circuit in August 2009, for which the Supreme Court also denied certiorari, on the same day as *Solvay*. On the issue of whether to impose *a priori* restrictions on the information that relators must have before filing a case, the *Ortho* holding is favorable to the relators, interpreting the “original source” standard of § 3730(e)(4)(B) to only require the relators to voluntarily provide the information to the government prior to filing of *qui tam* suit, as oppose to before public disclosure of the potential fraud.<sup>66</sup> However, the First Circuit’s discussion of circuit splits indicates a confusion of the law and a lack of uniformity between different jurisdictions that would be helped by a Supreme Court’s hearing of the case. In contrast to the more permissive First and Fourth Circuit, the relators face a much higher bar in making their case under FCA in the jurisdictions with more restrictive rules, such as the Ninth, Sixth, and D.C. circuits. The lack of a national standard for the use of FCA to regulate pharmaceutical promotion, a national activity, may result in inefficiency of enforcement and forum shopping, weakening the law’s effectiveness and reducing its fairness.

To partially counter these recent court rulings that narrow the power of the False Claims Act, Congress passed the Fraud Enforcement and Recovery Act (FERA) in 2009. The FERA

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<sup>66</sup> 579 F.3d at 26.

expanded the substantive liability sections of the FCA and increased the Government's ability to investigate and engage in discovery of potential false claims before bring a lawsuit.<sup>67</sup> The amendments softened the impact of *Solvay* on relators' ability to file suit by striking the "presentment clause" of § 3729(a)(1); the new provision imposes liability on anyone who "knowingly presents, or causes to be presented a false claim," without requiring that the claim be presented to an officer or employee of the U.S. government.<sup>68</sup> The new law also extends anti-retaliation protection to whistleblowers, providing them with a safe harbor and preventing industry-wide employment-lockout, which occurred with relative frequency to previous whistleblowers.<sup>69</sup>

Recent developments of the law, splits between circuits, and the battle between the judiciary and legislature makes one wonder there is something intrinsic to the FCA that is causing the confusion. The FCA was enacted in 1863 with the "principal goal of stopping the massive frauds perpetrated by large [private] contractors during the Civil War."<sup>70</sup> Although it has evolved over the past century-and-a-half, it is questionable whether the FCA is suited for addressing the problems of off-label marketing.

The purpose of the FCA's *qui tam* cause of action has been to allow insiders with specific information to come forward and pursue claims. This is in line with the legislative history of the FCA and its expansions which tried to find "the golden mean between adequate incentives for whistle-blowing insiders with genuinely valuable information and discouragement of

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<sup>67</sup> Robert Vogel, 2009 Amendments to False Claims Act, (2009) [http://www.false-claims-act-health-care-fraud-whistleblower-attorney.com/articles/2009\\_Amendments\\_FCA.php#](http://www.false-claims-act-health-care-fraud-whistleblower-attorney.com/articles/2009_Amendments_FCA.php#).

<sup>68</sup> *Id.*

<sup>69</sup> David Voreacos, *Grassley Asked Pfizer, Drugmakers How They Treat Whistleblowers*, Bloomberg Businessweek, (July 01, 2010). <http://www.businessweek.com/news/2010-07-01/grassley-asks-pfizer-drugmakers-how-they-treat-whistleblowers.html>.

<sup>70</sup> *Vt. Agency of Natural Res. v. United States ex rel. Stevens*, 529 U.S. 765, 781 (2000).

opportunistic plaintiffs who have no significant information to contribute of their own.”<sup>71</sup> While the FCA has been very effective in attaining judgments for health care fraud – \$14.3 billion since 1986-2008 when the FCA was revived and expanded – *qui tam* suits on off-label pharmaceutical promotion comprise only a very small proportion of this. To put these totals in perspective, the Department of Justice estimates that enforcement by the Medicare Fraud Strike Force, a multi-agency team of federal, state, and local investigators,<sup>72</sup> in the Miami area alone reduced medical billing by over \$2 billion dollars. The problem of false billing by physicians and hospitals dwarfs all medical off-label marketing suits, which totaled \$3 billion in the same period for the entire US.<sup>73</sup>

Prominent *qui tam* suits are more typically like the case against Johnson and Johnson settled on the 15th of January, 2010:<sup>74</sup>

The United States alleges that, in order to induce Omnicare and its pharmacists to recommend J&J drugs, the company paid kickbacks to Omnicare in numerous ways. First, the complaint alleges that J&J entered into agreements with Omnicare by which Omnicare was entitled to increasing levels of rebates from Johnson & Johnson so long as Omnicare implemented specific programs to increase the prescriptions of J&J drugs. Second, the

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<sup>71</sup> *United States ex rel. Springfield Terminal Ry. v. Quinn*, 14 F.3d 645, 649 (D.C. Cir. 1994).

<sup>72</sup> Department of Justice Press Release, *Medicare Fraud Strike Force Charges 94 Doctors, Health Care Company Owners, Executives, and Others for More Than \$251 Million in Alleged False Billing*, (July 16, 2010), [http://www.fbi.gov/pressrel/pressrel10/medicarefraud\\_071610.htm](http://www.fbi.gov/pressrel/pressrel10/medicarefraud_071610.htm).

<sup>73</sup> Department of Justice Press Release, *Assistant Attorney General Tony West Testifies Before the Senate Judiciary Committee Entitled “Effective Strategies for Preventing Health Care Fraud”* (Oct 28, 2010), <http://www.justice.gov/dag/testimony/2009/dag-testimony-091028.html>.

<sup>74</sup> Department of Justice Press Release, *U.S. Files Suit against Johnson & Johnson for Paying Kickbacks to Nation’s Largest Nursing Home Pharmacy*, (Jan 15, 2010), <http://www.justice.gov/opa/pr/2010/January/10-civ-042.html>.

complaint alleges that J&J paid Omnicare millions of dollars for "data," much of which Omnicare never provided. According to the complaint, the true purpose of these payments was to induce Omnicare to recommend J&J drugs. Third, the complaint alleges that J&J made various other substantial kickback payments to Omnicare, calling the payments "grants" and "educational funding," even though their true purpose was to induce Omnicare to recommend J&J drugs.

This Johnson and Johnson case is the kind of case which a relator can bring, even if the government later joins the suit and collects the lion's share of the damages. It involves quid pro quo payments to influence prescribing decisions, regardless of FDA label. The case turned around specific payments and rebates, payments for services which was never provided, and false payments labeled grants and educational funding, in contrast to the complexity of *Solvay* and *Ortho*, which required access both to the marketing activities of pharmaceutical companies and the prescribing habits of physicians. The relators need to prove intent, action, and effect, which is virtually impossible for any single insider who is not at the executive level. As a result, while in an ordinary year tens of millions of dollars is paid to relators under FCA claims,<sup>75</sup> almost none of this is for off-label marketing not involving kickbacks; instead the bulk is for fraudulent claims filed by doctors.

The numbers show that the FCA is effective primarily in dealing with criminal wrongdoing involving false claims filed and kickbacks. The following table was compiled by the law firm of Fried Frank from DOJ Civil Division records, and shows a breakout of recoveries from healthcare fraud enforcement action between *qui tam* and non-*qui tam* suits.

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<sup>75</sup> Note in 1996 the number of health qui tam suits doubled from 87 to 179, and two years later the qui tam awards jumped from \$9 million to \$58 million, and have varied between a low of \$45 million and a high of \$285 million in 2003.

Year	Actions		Recoveries			
	NQT	Qui Tam	NQT	Qui Tam DOJ	Relator Share	Total of All
1987	12	3	11,361,826	0	0	11,361,826
1988	8	5	2,182,675	355,000	88,750	2,537,675
1989	20	16	350,460	5,099,661	50,000	5,450,121
1990	27	11	10,327,500	903,158	119,474	11,230,658
1991	22	12	8,670,735	5,420,000	861,401	14,090,735
1992	29	15	9,821,640	2,192,478	446,648	12,014,118
1993	22	38	12,523,165	151,760,404	22,946,101	164,283,569
1994	43	76	381,470,015	6,520,815	1,185,597	387,990,830
1995	27	87	96,290,779	85,681,789	14,803,782	181,972,568
1996	20	179	63,059,873	51,576,698	9,374,568	114,636,571
1997	49	274	351,440,027	579,079,581	58,872,855	930,519,608
1998	35	275	40,107,920	258,638,736	47,822,301	298,746,656
1999	28	315	38,000,792	408,128,379	45,492,385	446,129,171
2000	36	211	208,899,015	725,011,203	115,759,246	933,910,218
2001	35	177	435,849,179	900,260,345	147,318,543	1,336,109,524
2002	24	194	74,567,427	961,248,757	154,289,403	1,035,816,184
2003	26	219	536,834,879	1,312,296,030	284,670,601	1,849,130,909
2004	28	275	34,816,447	475,370,142	97,434,278	510,186,589
2005	34	271	204,821,548	912,927,980	122,673,758	1,117,749,528
2006	18	223	1,050,520,714	1,241,774,802	166,735,688	2,292,295,516
2007	24	202	465,052,993	1,065,800,181	155,129,755	1,530,853,174
2008	60	228	150,808,253	966,568,225	183,528,337	1,117,376,478
2009	627	3,306	4,187,777,862	10,116,614,364	1,629,603,471	14,304,392,226

This table dramatically overstates the share of *qui tam* recoveries, since non-*qui tam* judgments do not include the recovery to the Social Security or Medicare trust funds, and many non-*qui tam* suits are settled at the district level by the U.S. Attorney's office, not centrally by DOJ's Civil Enforcement. Compared to the figures for non-*qui tam* judgments, the total for relators in off-label marketing as a share of the above numbers comes to less than \$100 million, the bulk from a few high profile cases.

FCA claims generally have to be pursued by the Department of Justice and are neither swift nor certain for drug marketing claims. While there is generally a two year lead time between suit and judgment, *qui tam* cases can involve off-labeling marketing that happened a decade ago, such as the recent DOJ settlement with Novartis over the marketing of a cystic fibrosis drug that began in 2001.<sup>76</sup> While there have been cases of corporate officers prosecuted for knowingly pursuing fraudulent billing activities, these are not associated with any of the large judgments mentioned earlier. This time-lag between activity and judgment opens the door to a cost-benefit analysis on the part of individuals employed in the industry, including executives and managers, in favor of engaging in off-label marketing: they might not be caught, and by the time the financial penalty occurs, even if it is a net negative for the corporation they work for, they might well have sold their own personal stake in the company, or moved on professionally. The FDA does not have the resources to mount long civil prosecutions by itself, as they take years, and therefore lack the individual deterrent effect in the case of marketing.

## **A Welter of Jurisdictions**

By making the Fraudulent Claims Act, with its focus on recovery of damages and law

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<sup>76</sup> See *Novartis Settles Off-Label Marketing Case*, (May 5th, 2010), <http://www.newsinferno.com/archives/20112>.

suits the centerpiece of enforcement after warning letters, which, it must be underlined, have no legal force, and do not commit the agency to any legal action, another negative effect has been created: that of a proliferation of jurisdictions where drug marketing suits are brought, and the resulting range of law, which varies from Federal Circuit to Federal Circuit on key issues, and involves state as well as Federal law. Thus suits can be brought in state courts, any federal district court, or adjudicated before councils established under several acts that amend the FD&C.

The first possible venue is in state courts, similar to the regime contemplated in the Medical Device Safety Act of 2009,<sup>77</sup> which allows lawsuits to be originated in state courts under state commercial statutes. This method has the advantage of dispersing the workload of enforcement and having regionalization of judgment based on local community standards of practice and advertising. This is the standard procedure for malpractice today. But this is not completely assured because of the possibility that state proceedings will be pushed to Federal Court under diversity of jurisdiction under the Erie rule. Because manufacturers are localized in a few states, while potential plaintiffs are in all states, there is a good chance of diversity of jurisdiction.

However, its defects are severe: it defeats uniformity, it assures no particular level expertise, and no balancing of protection and access, and it undermines the Federal structure contemplated by congress, encourages under-marketing in strict jurisdictions, and over-marketing in permissive ones, and places local and parochial state interests in the mix of decisions. Would a state court decide against a local drug maker, and in favor of one in another state?

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<sup>77</sup> Medical Device Safety Act, H.R. 1346, 111<sup>th</sup> Cong. (2009).

The larger problem is that of the possible grounds for action, state courts cannot judge FD&C claim, and have varying statutes on False Claims Act for Medicare, based on the Deficit Reduction Act of 2005,<sup>78</sup> which sets standards for state False Claim Acts and recovery of amounts as the result of state action. The state is required to:

- Establish liability to the State for false or fraudulent claims described in the False Claims Act (FCA) with respect to any expenditures related to State Medicaid plans described in section 1903(a) of the Act;
- Contain provisions that are at least as effective in rewarding and facilitating qui tam actions for false or fraudulent claims as those described in the FCA;
- Contain a requirement for filing an action under seal for 60 days with review by the State Attorney General;
- Contain a civil penalty that is not less than the amount of the civil penalty authorized under the FCA.

As of May 2011 the following states have been reviewed by the Office of the Inspector General of HHS for compliance with these Federal Provisions: California, Colorado, Connecticut, Delaware, Florida, Georgia, Hawaii, Illinois, Indiana, Iowa, Louisiana, Massachusetts, Michigan, Nevada, New Hampshire, New Jersey, New Mexico, New York, Oklahoma, Rhode Island, Tennessee, Texas, Virginia, Wisconsin.<sup>79</sup>

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<sup>78</sup> Deficit Reduction Act of 2005, Pub. L. No. 109–71, §6031, 120 Stat. 4, enacted February 8, 2006.

<sup>79</sup> Office of the Inspector General, *State False Claims Act Reviews*, <http://oig.hhs.gov/fraud/falseclaimsact.asp>.

Lanham Act<sup>80</sup> claims can be pursued in state courts, for example by having commercial codes which expressly enforce federal law, and therefore create another potential for lack of uniformity based on how each interprets enforcement. These state cases are often precluded by conflict with a more specific federal statute, see *VP Racing Fuels, Inc. v. General Petroleum Corp.*, where claims under the Lanham Act were precluded based on a conflict with Petroleum Marketing Practices Act.<sup>81</sup> However, this is not a blanket preclusion; the specific claims must be evaluated, to see if there is a specific conflict. In *Pom Wonderful LLC v. Ocean Spray Cranberries, Inc.*, the court ruled that the Lanham Act claims were not precluded by the FD&C.<sup>82</sup>

## Summary

Against the complexity of the policy balancing act, of protecting the public's twin interests in having access to as many beneficial drugs as possible, while protecting patients from dangerous medications and useless expense, the legal regime of off-label marketing is inefficient, legally ineffective, and constitutionally suspect. The primary means of enforcement, an escalation from warning letters to civil and criminal suits, takes years to work through the system, and seems to have little overall effect on the practice of marketing drugs for uses which are dangerous or useless. The attempt to directly limit marketing has repeatedly been frustrated by the *Central Hudson* standard required for restrictions on commercial speech in a chain of cases starting with *Washington Legal Foundation v. Friedman*,<sup>83</sup> and the subsidiary attempts

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<sup>80</sup> Lanham Act, 15 U.S.C. §1125(a).

<sup>81</sup> *VP Racing Fuels, Inc. v. Gen. Petroleum Corp.*, 2009 WL 4282124 (E.D. Cal. 2009).

<sup>82</sup> *Pom Wonderful LLC v. Ocean Spray Cranberries, Inc.*, 2009 WL 2151355 (C.D. Cal. 2009).

<sup>83</sup> *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d. 51 (D.D.C. 1998).

using the False Claims Act as a ground for private action have produce no high profile victories, and a string of decisions restricting the practical applicability of the FCA.

As a consequence, it is time to propose more sweeping changes to the legal regime associated with drug marketing. However a large part of the problem has been the framing of the legal issues as agency against marketing efforts and pharmaceutical corporations, rather than as a cooperative effort of public agency and private industry to maximize the total public good. To see how best to pursue this goal, it is useful to invoke concepts from economics, specifically the theory of games, to expand the quantity and improve the quality of information available to physicians, researchers, the government, and the consumers of pharmaceuticals.

### ***A New Legal Regime for Drug Marketing***

The proposed new regime rests on three elements, all of them already present in embryo in the law. The first is a formalized multi-tier labeling system from the FDA, which would take the range of exceptions already present in practice and in the FDAMA and produce a single clear stepped system of labeling. The third is to expand the authority given by the Prescription Drug Marketing Act to allow the FDA to have enforcement powers that would be swift, sure, and effective in the presence of non-compliance by manufacturers. The purpose is to provide a better intermediate range of Agency responses between those needed in large violations and the smaller administrative actions in the case of minor disputes over the scope of the label. The first then, offers a series of carrots for compliance, and the second, a stick which will press drug companies to cooperate in good faith with the agency.

### *Standards of an Effective Legal Regime*

The desire for regulatory uniformity is based on three considerations. The first comes from the regulatory chaos that would ensue if there were an unspecified number of local systems, including potentially one for each state, and possibly more if differences among localities are allowed. Since drug marketing is a national activity, pharmaceutical manufacturers would face a nightmare of local regulations, which they could violate simply by buying internet advertising or air time on a station that covers more than one jurisdiction in its broadcast area.

The challenge of navigating multiple state and local standards of marketing could at best induce “defensive marketing” where there is a convergence of adherence to the strictest standards when costs of tailoring of marketing outweighs the benefits gained from lower standards, and more likely result in regulation confusion and uncertainty. Both of these outcomes drive up the costs of compliance without necessarily keeping physicians and patients better informed. Since the goal is to present the information on the drug truthfully and accurately, defensive marketing has the drawbacks of defensive labeling—misrepresentation, information overload, and marketing drought. In such “a race to the bottom” toward the most conservative marketing standard, the marketing is either going to be skewered toward narrowing presenting the label, excessively emphasize the negative effects, or alternatively give up marketing completely because the risk and liability and costs exceeds the benefits and profit. Nether of these effects would further the public good of informed physicians and patients.

The second consideration is the manifestly irregular level of enforcement. Such a system would create a lottery where by manufacturers are subject to civil litigation or enforcement in some jurisdictions and be spared in others, facing disproportionate fines or consequences. The

companies would, here to fore, avoid doing business in areas of more stringent rules and enforcement or limit their marketing only to that which would be acceptable in the most restrictive sense. If there are 50 jurisdictions there is the potential not merely for differing standards, but contradictory ones. If federal regulations can be disregarded by lawmakers, officials, judges, and juries, there is the potential for eroding the confidence and authority of the entire federal scheme. It is clearly the objective of the Congresses that have passed and amended the Food, Drug and Cosmetic Act that there be a single national standard for the approval and manufacture of drugs, and this implies that there be a single and uniform flow of information.<sup>84</sup> For example the way that Herrmann and Bownas have argued in their 2009 paper that the FDA label should be completely inadmissible as evidence for malpractice standard of care.<sup>85</sup> If the label provides no evidentiary weight, why should a manufacturer not push the envelope in promoting off-label uses? Indeed the uniformity of labeling that is part of the structure of FDA regulation almost requires that claims made on the basis of FDA approval be presented in a uniform manner.

This leads to the importance of the FDA as an expert agency, and one which is capable of balancing both potential harm and potential benefits. In a locality, particularly a jury trial, the individuals harmed are present as the plaintiffs, but the individuals whose lives have been saved or improved will not be present to rebut or balance the presentation of the harms alleged. By lodging the decision making process in an expert agency with national scope, the government

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<sup>84</sup> David A. Kessler & Wayne L. Pines, *The Federal Regulation of Prescription Drug Advertising and Promotion*, 264 JAMA 2409, 2410 (1990).

<sup>85</sup> Mark Herrmann & Pearson Bownas, *Keeping the Label Out of the Case*, 103 Nw. U. L. Rev. Colloquy 477 (2009), <http://www.law.northwestern.edu/lawreview/colloquy/2009/20/LRColl2009n20Herrmann&Bownas.pdf>.

can argue both for the protection of the public from misleading or erroneous claims, and for the access of the public to the most current and complete information on treatment options.

This centralization has the further advantage that the true costs and benefits of a given regulatory regime can be monitored and measured, allowing manufacturers, policy makers, and the public to judge whether the regulatory regime is, in fact, effective and efficient at promoting the desired ends, and is, in fact, promoting the desired results. While centralization imposes further costs on the agency charged with maintaining the national system, it also allows the offsetting fees or other charges to be centralized as well, and tells Congress exactly how much it costs to enforce their legislation, and the Executive Branch how well its policy regime is faithfully executing the laws.

The next principle of a best solution is that marketing claims should be directed at telling the truth, the whole truth and nothing but the truth. This means that it should discourage both manufactures from promoting misleading, unproven, or confusing claims, and conversely from engaging in defensive marketing which could frighten or confuse the public and physicians. While on balance the evidence indicates that presently there is an under-reporting of dangers and side effects, neither over, nor under reporting advance the public good.

Finally, since drug and device research and manufacture are for profit in a large majority of cases, the inability to market a product virtually assures that it will not be profitable. This could deter the research into treatments which might be subject to any number of claims, and thus deny the public access to treatments which have been judged safe and effective for their intended population, or new potential treatments in the future. This means that any procedural regime should be judged on its ability to protect the public from harm, and promote the public

good. A treatment that a person does not receive because their physician did not know about it is worse than one which is not available at all. This is not only because of the human tragedy of needless death or suffering, but from the reality that the research and manufacture of drugs is largely composed of fixed costs, by reducing by one the number of beneficiaries, it increases the cost that must be apportioned on the remaining recipients of the drug.

The FDA recognizes that prescribing of drugs for unapproved uses is important in the exploration and expansion of medical knowledge. As Joseph, Deaton, Ehsan and Bonanno outline in "Enforcement Related to Off-Label Marketing and Use of Drugs and Devices: Where Have We Been and Where Are We Going," the government recognizes that medical evidence often moves faster than regulation, and explicitly allows physicians to act on sound judgment and evidence.<sup>86</sup> Medicare and Medicaid compensate for unapproved uses of drugs. These treatments form the basis of potential expansion of labeling, new uses for old drugs, and new categories of drugs. Without this empirical basis, the introduction of new applications would be hindered.

As noted earlier, the most difficult task for a manufacturer is distinguishing direct from indirect promotion for off-label uses, which are not permitted by FDA, as opposed to communicating about off-label uses in a strictly non-promotional and scientific context, which is permitted commercial speech.

Clarity is important, because it is essential for individuals to know, or be able to know, in advance, whether a particular action is legal or not. The current state of marketing enforcement of drug and device law fails to meet this most basic of fairness in law.

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<sup>86</sup> John N. Joseph et al., *Enforcement Related to Off-Label Marketing and Use of Drugs and Devices: Where Have We Been and Where Are We Going*, 2 J. Health Life Sci. L. 73, 98–105 (2009).

Because unapproved uses represent the future state of the art, a legal regime should not throttle in the cradle potential life saving and life improving applications, and drug companies should feel confident that wonder drugs that have many potential applications will have the chance to prove their worth. Patients whose prognosis is poor have less to lose than those who are not in urgent danger, or facing chronic debilitation. In the present regime, it is very difficult to weigh efficacy against risk for patients. Marketing considerations should not interfere with the practice of medicine, or with the dissemination of legitimate medical experience and data on the efficacy and safety of already approved medications.

This differs in degree from the promotion of drugs for unapproved application, for example the use of anabolic steroids for athletic performance enhancement, or human growth hormone for cosmetic reasons. Where the exact line between life improving use, and high risk abuse is, cannot easily

In summary, uniformity, expertise and balance, veracity, and promotion of the public good both for protection and treatment provide a framework for reasoning towards a procedural regime for the enforcement of marketing regulations in the field of drugs and medical devices.

These principles follow from well established legal theory on the approval, regulation, and enforcement of drug and device law. For example the testimony of Peter Barton Hutt before Congress on the Medical Device Safety Act of 2009, contains virtually all of the principles in arguing against the decentralization of device liability.<sup>87</sup> The same principles apply to the marketing of drugs and devices because the same liability is involved for misapplication or misuse.

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<sup>87</sup> Testimony of Peter Barton Hutt before the Committee on Health, Education, Labor, and Pensions, United States Senate on S. 540 The Medical Device Safety Act of 2009 (August 4, 2009). <http://help.senate.gov/imo/media/doc/hutt.pdf>.

## **An Economic View of the Structure of Marketing and Labeling**

One of the most important considerations in any legal proposal is asking how the regime will play out in actual practice. It is not enough to make statements out of ideological bias as to how a particular regime will operate in actual practice. In aid of analyzing the problems with the current regime, and with proposing a new one, some concepts from the Theory of Games are introduced here to give an analytical tool that can survive not only academic rigor, but practical application.

The Theory of Games is a formalism for examining decisions under different pressures of outcomes that rely upon information and the actions of other actors. Game theory models decisions when actors have choices, but their final outcome relies on the decisions of others. Game theory provided insights into, for example, why competitive actors could end up at the worst, rather than the best result, and how an actor with an advantage in information could produce worse results for that actor. The first one is exemplified by the famous Prisoner's Dilemma, and the second by work on "information asymmetry."

Game theory has been proposed as a mechanism for examining the law, in that it provides several compelling advantages. The first is that it relates to other disciplines, the second is that game theory forms can be described as fact patterns, and are thus open to legal reasoning, and third they offer a dramatic simplification of problems. In *Game Theory and the Law*, Baird, Gertner and Picker argue:

Game theory, like all economic modeling, works by simplifying a given social situation and stepping back from the many details that are irrelevant to the problem at hand. The test of a model is whether it can hone our intuition by illuminating the basic forces that are at work, but not plainly visible when we look at an actual case in all its detail. The

spirit of the enterprise is to write down the game with the fewest elements that captures the essence of the problem.<sup>88</sup>

But most importantly they provide a way to counter immediate judgments and biases, for example in "Law and Game Theory," Eric Rasmusen describes one paper this way:

The last section of this volume consists of three articles about the behavior of courts. The first article, "The Selection of Disputes for Litigation" (George Priest and Benjamin Klein, *The Journal of Legal Studies*, 1984), is famous for destroying the common-sense—but false—idea that if defendants win most of the cases in a court, that court is pro-defendant. This is false because what may be happening is that the court is so pro-plaintiff that only the defendants with extraordinarily strong evidence on their side bring their suits to trial, or because the majority of cases filed settle in favor of the plaintiff but the few that reach trial are a special set which happens to include mostly cases that the defendant will win.<sup>89</sup>

In game theory, the possibilities are represented by a table, with the choices available to each player presented as columns or rows. The intersection of two choices is found by looking across the row representing one player's choice, and finding the intersection of the row that represents the other player's choice. The consequences for each player are there. Games can have results that are known in advance, or not, they can be fixed, or variable. What is important is the narrative of choices can be turned into a fact pattern, and the results of that fact pattern

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<sup>88</sup> Douglas G. Baird et al., *Game theory and the Law*, 7 (1998).

<sup>89</sup> Eric Rasmusen, *Law and Game Theory*, 10 (2006).

<http://www.rasmusen.org/published/Rasmusen-07-book.lawgames.pdf>.

extrapolated.

Consider, for example, two parties to a law suit, each party has different positions and interests, as well as differing abilities to pursue a suit. They can settle their differences, or take them through the trial process. If both actors cooperate, they can come to a settlement which is most beneficial to both; however, either party can, assuming a sufficiently strong case and enough resources, force a trial. This produces a table with probable outcomes, and allows each party to make a rational decision whether their best personal outcome is settlement or trial; however, this might not produce the highest expected return for both. Since policy is interested in maximizing the probable outcome of encounters with the law, and has the ability to set the probable outcomes, policy can alter the very terrain of the decision, for example, by forcing discovery, so that no party has a sufficient information advantage to deny the other a rational choice, and so that no party fears not having information, and so choosing to go to trial from fear that the other party is hiding crucial details; nor should any party fear to exercise their legal rights in pursuit of their interests.

The tools from economics that this paper will rely upon come then, from 70 years of development of game theory and economics. The first is two forms of game, the Prisoner's Dilemma and the related form, the Stag Hunt. These are kinds of "games" where two more participants are faced with a decision to cooperate, or betray, each other, and there are different expected results in each case. The second is the concept of an information asymmetrical "death spiral," outlined by Akerlof,<sup>90</sup> where the presence of bad goods in a market leads to a gradual driving out of better goods.

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<sup>90</sup> George A. Akerlof, *The Market for 'Lemons': Quality Uncertainty and the Market Mechanism*, 84 *Quarterly Journal of Economics* 488, 492–94 (1970).

The classic explanation of the Prisoner's Dilemma<sup>91</sup> is, in fact, phrased as a legal one: two men are caught fleeing the scene of a robbery; the police present both with a series of possibilities. The first is if both maintain their innocence, then they will both be sentenced to a year in prison. If one talks, then that one will go free; the other will serve 7 years. If both talk, then both will serve 5 years. Each one reasons as follows: if the other does not talk, then either I will serve one year for not talking, or none for talking, so I should talk, and if the other talks, then I will either serve 7 years if I do not talk, or 5 if I do. That means, either way, I am better off talking than not talking, leading to both talk, and both go to prison for 5 years, which is the worst total outcome, because a total of 10 years are served, as opposed to 2 or 7. The ironies to this are that, presuming both are guilty, then the society wants there to be a dilemma, but the same reasoning applies even if one is innocent.

Economic theory provides a variety of answers to the Prisoner's Dilemma. In the case where the outcomes cannot be changed, these include signaling or other penalties, for example, a promise to the other to seek revenge later if the other rats. However, if the outcomes can be changed, by, for example the law, then it is possible to change the form of the game from one where the best choice is to betray, to forms where the best choice is to cooperate. One of these cooperation friendly forms is the Stag Hunt.

A Stag Hunt is a similar either or decision, but instead, two hunters have a choice, both can hunt a stag, which is worth 7 days of food to both if the both hunt for a stag, or one can hunt rabbits alone, which is worth 2 days of food if the other hunts a stag, but only 1 if both hunt rabbits. In this case, cooperating is always better than not cooperating, so both cooperate.

The other objective is to promote what is called “robust” cooperation, rather than

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<sup>91</sup> Robert Axelrod, *The Evolution of Cooperation*, 7–15 (1984).

“fragile” cooperation. In economics “fragile” defines a situation where relatively small changes in the distribution of strategies, preferences, or conditions create a very large change in results, whereas robust describes the opposite: one where small changes to conditions lead to small changes in results.<sup>92</sup> In Brown and Vincent's 2008 paper, they explore what conditions lead to stable cooperation in different games. They conclude that the key criterion is the uncertainty of maximum rewards and penalties.<sup>93</sup> Where these are known, actors come to robust cooperative arrangements, and where they are not, cooperative arrangements become unstable. Therefore, legal arrangements aimed at robust cooperation, should examine those cases where either rewards or penalties are prone increase without easily understood limits. The thrust of their argument is that known rewards create incentives to violate the norms of the group to attain them, and known penalties are simply computed in a cost-benefit way based on the potential known penalties, however, in the face of uncertainty and potential run-a-way consequences, self-interest leads to a collective understanding to limit potential damage.

This fits in with the well known effect called the "market for lemons." Consider a used car market, goes Akerloff's paper,<sup>94</sup> and assume there are two kinds of cars: lemons and good cars, and the sellers know which is which, but buyers do not. The sellers reason "if I offer a good car, the best I can do is sell it at the good car price, and I might get the bad car price, but if I offer the bad car, the worst that can happen is that I get the bad car price, and I might make the good car price." The buyers reason the same way, and offer only the bad car price. This means that the good cars will not be offered for sale as long as there are bad cars. A "death spiral" occurs when

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<sup>92</sup> Joel S. Brown & Thomas L. Vincent, *Evolution of Cooperation with Shared Costs and Benefits*, 275 Proc. Royal Soc'y. Biological Sci. 1985, 1993 (2008).

<sup>93</sup> *Id.*

<sup>94</sup> George A. Akerlof, *The Market for 'Lemons': Quality Uncertainty and the Market Mechanism*, 84 Quarterly Journal of Economics 488, 492–94 (1970).

each sale of a bad car convinces buyers that only bad cars are for sale and each sale of a good car at the bad car price convinces sellers it is not worth offering a good car for sale in this market. Good cars pile up, and so command a lower price even if the buyer offers a good car. The irony of the "market for lemons" is that the seller has an advantage in information, but is penalized for that advantage.

The challenge is to turn a Prisoner's Dilemma into a cooperative pattern, and to establish a robust cooperative pattern, which is not prone to break down precisely when dealing with the most consequential cases. To do this is to require diagnosing what the original problem was. It was not FDA administrative practice, or insufficiency of congressionally mandated specifics of the details of commerce, but instead the very design of a labeling scheme which has insufficient gradations, high barriers to entry of new uses, and a focus on the wrong part of pharmaceutical marketing for FDA enforcement. Thus, despite almost a quarter century of tinkering, Congress has failed to solve the problem, because the basic approach was one of attempting to micro-manage the FDA, and have the FDA micro-manage the industry. Another large omnibus reform is likely to run into the same problems as previous attempts: the first amendment law is not friendly to Congress restricting speech which is not fraudulent and is in pursuit of a lawful end, courts are not friendly to private entities bringing complex suits under the FCA, an act which is only tangential to the question, nor do are they involved in ordinary cases in telling companies what not to do to restrain abuses in marketing.

### **Proposed Regulatory Scheme: Tiered Drug Labeling**

The fact that there are insufficient gradations to labeling is widely recognized.<sup>95</sup> What is

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<sup>95</sup> Sidney A. Shapiro, *Limiting Physician Freedom to Prescribe a Drug for Any Purpose: The Need for FDA Regulation*, 73 Nw. U. L. Rev. 801, 814–18 (1978-1979).

required is to expand information by codifying the welter of exceptions, approval extensions, and conditions into a clearly delineated scheme, and attaching specific benefits to each labeling step, so that companies will have an incentive to focus on legitimate research intended to expand the label of the drug in question, or raise the level.

The tiered-labeling structure for marketed drugs should have several broad levels, with ability to incorporate particular additional information within each level, and is concise, clear, and code-able, to avoid information overload on one hand, and accurately characterize the level of evidence on the other. The vertical distance between each level will need to be set at intervals that will incentive the companies to conduct clinical research to generate more information on the drug's safety and efficacy. In a sense, the tiered system provides stepping stones over the gulf between the extremes of approval and non-approval, with the incentives to the pharmaceutical company for clinical testing more closely aligned with overall benefits of the drug, including both the public good of medical benefits and the private good of higher profits and expanded market. The company efforts will be redirected from hoping to find most effective, yet discrete way of engaging off-labeling marketing to productive R&D that would provide physicians, patients, and regulators with more information on the drug.

The proposed framework is to have several levels of FDA investigation and certification available, with specific benefits and restrictions for each, for drugs with at least one approved indication. Each level will be coded by color on the label: for instance, Approved would be Green, Reviewed would be Yellow, Developmental would be Orange, and Experimental would be Red. Unproven uses would be a kind of reverse labeling: for those cases where there is evidence that the medication should not be used in the target population, or for the particular

condition, as such it would be related to the present black label warnings. Uses that are “unapproved” in the tiered system will also alerts physicians and payors that level of clinical evidence is dubious or anecdotal at best, which will in turn encourage company to seek recognition of at least one of the intermediate levels if they intend to expand use of the drug within that particular disease area..

There will, however, still be a significant difference between the intermediate levels of labeling, and the approved status, so that the tiered system does not discourage pharmaceutical companies from seeking approval. Intermediate levels do not grant any additional market exclusivity, which is often the single greatest driver of companies seeking approvals for subsequent indications. While each higher level indicates stronger clinical evidence to support the drug’s use for an unapproved indication, they do not provide the same product liability preemption shield of a full approval, which though no longer an invincible defense since *Wyeth v. Levine*,<sup>96</sup> still has significant force when the specific event is clearly warned in the label. The reduced liability protection also would be apply to physicians in malpractice litigation, where intermediate levels will not receive the same level of deference in establishing the standard of care as a fully approved label. Perhaps, the differentiation that most directly impacts the product’s profitability is the formulary status of the drug: both private payor and Medicare/Medicaid would take into consideration the levels as a proxy for strength of clinical evidence when making that decision.

Reviewed uses are those which are similar to the common off-label practices which physicians routinely employ, for example, using a medication for a similar patient population (e.g., pediatrics) or condition (e.g., pathogenesis pathway). However, there are important safety

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<sup>96</sup> *Wyeth v. Levine*, 555 U. S. 555, 555 (2009).

implications for reviewed versus approved drugs. One of these would be to have a lower bar for black box warnings on delivery, dosage, and efficacy. In these cases the FDA would do as the label states: act as an honest broker, reviewing not only the pharmaceutical company's studies, but those from the field as well. In this way, the FDA could be guided by existing evidence based practice, and disseminate it as well. This would also dramatically reduce the need for off-label dissemination of studies and other cherry picking of information. The advantages that would accrue from being FDA reviewed would be a presumption against misbranding claims, and the ability to introduce the label as proof of compliance and a defense in medical malpractice.

Developmental indications are those for which there has been approval of the drug in a major foreign jurisdiction, such as the European Union or Japan, or for which there is clinical evidence for efficacy, without substantial evidence of increased risk. The purpose of the developmental indication would be to inform physicians of practice or research that indicates that there is substantial basis to use the drug for the indication, but that the data is still provisional, at least in the United States. Having this level will also encourage communication and share of information between the three major Drug approval agencies of the developed world, which would bring positive externalities (e.g., efficiency) to both the agencies and industry.

Experimental indications cover the cases of terminal patients, or those with extremely poor prognosis in general, who are seeking whatever glimmer of hope the medical profession offers. These would be restricted to target populations without alternative treatments, or for those whose alternative treatments do not offer a significant improvement to prognosis. The experimental rating will provide patients without alternatives with the option of trying drugs that

have reach a FDA-determined threshold level of safety and efficiency, and where the potential for benefits outweighing the risk. The tiered labeling scheme can be elaborated with several additional metrics that enhances its informativeness. These additional metrics will be coded and displayed next to the colored dot of the tiered levels, displayed in a clear and obvious manner, perhaps bolded in a green or blue box to both draw attention and prevent confusion with a black box warning. One such metric is the route of delivery, which as the facts of *Wyeth* suggested, a compound perfectly safe in one formulation can harbor significant risks in another.<sup>97</sup> Another to consider is a battery of basic patient information, such as gender, race, and comorbidities, for a population that is consider most beneficial as determined by the clinical trials. This follows the FDA's trend of granting narrow indications more frequently and gives the Agency an additional tool to specify the patient population that would most likely to benefit. Defining patient populations narrowly also has the benefit of encouraging more clinical studies, as pharmaceutical companies can only claim as much as they tested, and limiting the potential for abuse of cherry-picking patient sub-groups.

The new label can also have board indicators of safety and efficacy that might not be linked to a particular level, but signals to physicians and payors the strength of the evidence and the level of risk. Many of these indicators, such as REMS and Phase-IV study requirements, are already part of the FDA's post-marketing regulatory scheme and would be easy to incorporate into the new system. Others, for instance the recommendation for prior authorization of compounds with lower levels of evidence by private payors and Medicare/Medicaid, are novel mechanisms the Agency may employ to increase the regulatory effectiveness of the scheme. As

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<sup>97</sup> *Id.* at 555 (“Directly injecting the drug Phenegran into a patient's vein creates a significant risk of catastrophic consequences... The warnings on Phenegran's label had been deemed *sufficient* by the federal Food and Drug Administration (FDA)...”).

long as the Agency does not cross the line of regulating the practice of medicine, the Agency may make recommendation to the payors, since the approved label is already functioning in that capacity.

The intent is to communicate to physicians and patients that a drug, while not having gone through the full approval process, still has sufficient evidence to warrant use in appropriate courses of treatment. By creating a greater range of gradations, it removes the current haze of what is permissible off-label marketing, because, in this system, off-label really would mean off-label: prescribed by the physician solely on his own judgment.

<b><u>Label</u></b>	<b><u>Requirement</u></b>
<i>Approved</i>	Present regime, including safety trials and efficacy
<i>Reviewed</i>	Proof that the drug is the standard of care, backed by both empirical and clinical evidence independently gathered.
<i>Developmental</i>	Certified by the EU, or with substantial independent clinical evidence of efficacy and safety.
<i>Experimental</i>	Clinical evidence of efficacy
<i>Warning</i>	Substantial evidence that the medication is either ineffective, or unsafe for the particular indication.

This turns the present Prisoner's Dilemma of almost all or nothing approval, into a cooperative Stag Hunt, in that the agency is no longer faced with opening the gates entirely to the use of a drug for a particular indication, and the pharmaceutical company has the ability to

market indications where there is independent evidence that the drug is the standard of care based on clinical evidence. However, such a system would require that the FDA both have a greater reach, to more rapidly withdraw medications from the marketplace when there is indication of potential harm, and a venue with sufficient expertise to adjudicate the potentially knotty questions of level of approval.

How this happens may seem paradoxical. In the present system the agency's best approach for itself is to prevent approvals, or hold them to a high bar, to prevent high profile failures. An individual drug company's best strategy, given the high bar, is to pursue drugs which have as many hard to pin down off-label uses as possible, since these are the least likely to be identifiable in the case of liability, and those that are most over-prescribed. The least public benefit results: drugs are not approved, and companies as a group will tend to seek drugs in disease areas, such as pain management and psychiatry, since these are the most difficult to differentiate effective from ineffective, and to seek “niche busters” which are prescribed, as in the case of GERD, for anyone who is symptomatic, rather than based on evidence of efficacy. These are, then, the least useful indications. The triage of the company then is neither to seek approval for indications that will work, since these will happen in any event, nor for those that are obviously dangerous, but only for those indications which medical science would be unlikely to accept without marketing, instead of seeking approval where there are clear voids, since they know that if a medical treatment is efficacious, once approved, it will be adopted anyways as a standard of care over time with only minimal input, and it will be hard to dislodge if later research calls it into question.

As the example of pediatric GERD shows, there can be the FDA label, which does not

match professional guidelines, which does not match clinical practice and what is shown to be effective when studied; none of the sources of authority agrees with each other. The purpose of expanding the FDA's role as a broker of information is to guide more physicians not only to best practices, but to spur constant improvement on best practices. In the GERD example, the APA guidelines would have formed the basis of an FDA Reviewed label, meaning that companies could market this without fear of accusations of misbranding or "off-label" marketing, and the study on clinical results could have been used as the basis for an application of an "Experimental" label with a follow up study. Conversely, these studies would be designed to separate the 25% of the patient population who would show improvement, from the others, who were either not helped, or were harmed, by the present usual course of treatment.

The second two pieces of the proposed regime are designed to shift enforcement efforts away from adversarial and long suits, and towards cooperative engagement, but backed by swift and sure inducements to comply. They deal with a problem implicitly described above, but which again is easier to describe as a game theory pattern. One of the important distinctions in game theory is between single games, where actors have the incentive to maximize a single play, or conversely minimize loss, to games where there is an incentive to seek a stability, the basic form of which is called a Nash Equilibrium.<sup>98</sup> For most drugs, the reason that warning letters and other signs of FDA displeasure are sufficient to induce compliance, because the FDA and the company are involved in a repeated game, the Nash equilibrium strategy is to treat the other side as it has treated you, a strategy of a family known as "Tit for Tat" strategies, where the opening move is to

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<sup>98</sup> John Nash, *Equilibrium Points in N-Person Games*, 36 Proc. Nat'l Acad. Sci., 48, 48–49 (1950).

trust, and then respond with the other side's most recent move.<sup>99</sup>

However, a blockbuster drug is different. A single such drug can make the careers of the individuals creating it, and the revenues for these drugs are so large, that even if there is a billion dollar penalty waiting, the incremental revenues will more than pay that fine. Also, larger pharmaceutical firms that produce most of the blockbuster drugs have a regulatory advantage, because they are more likely to be high volume New Drug Application (NDA) filers and early market entrants due to their abundant resources and experience navigating FDA's approval process, both factors shown to lead to regulatory protectionism.<sup>100</sup> Thus, the maker of a drug that has the potential to be a blockbuster drug has every reason to attempt to betray the system, and wait for the FDA to catch up. In this tiered labeling model, instead of tit for tat producing minor negative steps of betrayal, it will produce "rabbit hunting" of small advantages. The public is better off, even if nothing else changes.

There is then a series of carrots, to go with the greater use of sticks. These sticks should be seen in the context of the more nuanced labeling system proposed, namely that there will be a broader ranges of labels, and a broader range of marketing within these tiers. So long as the broader indication is both labeled clearly in each section as the header, with the color coding, and if needed a black box warning on administering the drug for the sub-approval levels of labeling, there is no reason for prior restraint, and no reason to have regulations or restrictions, such as the "unsolicited request" rule, which invite abuse. The Agency will have less hesitation in exacting penalties, since they will have a more nuanced range of responses in moving labeling, and can immediately respond to questionable marketing by updating the label to warn against the use.

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<sup>99</sup> Robert Axelrod, *The Evolution of Cooperation*, 13–14 (1984).

<sup>100</sup> Daniel P. Carpenter, *Protection without Capture: Product Approval by a Politically Responsive, Learning Regulator*, 98 Am. Pol. Sci. Rev. 613 (2004).

Physicians, and payors, will have the ability to enforce the label through the normal mechanism of their gatekeeping powers.

The unexpected result, then, is that the way to turn the approval “game” into a Stag Hunt is to create rabbits. Remember that the choices in a Stag Hunt are cooperate for greater good, or not cooperate for lesser good, and if both fail to cooperate, for the least good for both. By creating tiers that can be pursued more or less independently by both players, the Agency can promote the public good without reference to the companies, and the companies can, by incremental stages, promote medically valid uses of their products. By creating rabbits, the preconditions for a robust game are created: each side knows that if the other stops cooperating, it can pursue independent good. Instead of attacking off-label marketing, the Agency will be able to set a path towards an indication being valid; instead of seeking to approve medicines of hard to prove disutility, it will have ways of expanding utility. Third party beneficiaries can also promote expansion of indication, which the Agency could encourage, by extending liability umbrellas over these indications.

The key would be to reframe the guidelines as "voluntary" but place substantial restrictions on those companies who abused them, as well as offer a safe harbor for those that comply. In addition to being able to force products to include information as part of the label, the FDA is free to restrict the distribution of medications. This would allow the agency to press much farther in its guidelines. There is no First Amendment issue, if companies agree to restrictions in return for concrete advantages.

The virtues of this system are obvious: it creates incentives to provide information, rather than attempt to manufacture it by buying professional recommendations and journal articles,

since the very process of moving from journal to marketing would be one which the Agency would have oversight of. The practice of paying specialists, who then make recommendations, undermines the confidence in the system. For example, it has recently been reported that the doctors who made recommendations to stockpile anti-virals in response to H1N1 and Swine Flu, had a fiduciary relationship with the manufacturers of these medications.<sup>101</sup>

The present labeling is used to make judgments on malpractice and on coverage under insurance. However, because of the lack of granularity of the licensing system, and the lack of a clear congressional scheme to make labeling fill these functions, courts have often deemed off-label neither to be an indication of malpractice, nor grounds to deny coverage. In the regime proposed, the labeling system would possess this granularity, and suits could with greater confidence use the specific use against the labeled indication in making these judgments. The Agency could go farther and make particular indications recommended for "prior approval" by insurers.

The concerns this scheme raises are the application of the *Central Hudson* doctrine, the potential of opportunistic law suits, and the potential expense. Each of these concerns is squarely addressed by the regime proposed. It avoids direct confrontation with *Central Hudson*, relying primarily for enforcement on the FDA's congressional mandate to regulate the interstate commerce of pharmaceuticals. It proposes a theory of damages for private enforcement which is directly linked to material damages caused by improper marketing based on an interest created by holding a license, which would prevent standing from the vast majority of opportunistic suits. Finally the cost to the companies can easily be regained, since the sub-approvals could be

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<sup>101</sup> Deborah Cohen & Philip Carter, *WHO And The Pandemic Flu "Conspiracies."* 340 Brit. Med. J. c2912 (2010).

immensely profitable, and reduces, rather than increases, their risks.

The proposed labeling scheme avoids the problem of directly confronting *Central Hudson*, since distribution is firmly within the Interstate Commerce Clause.<sup>102</sup> The First Amendment issue is well known to those who follow drug marketing, and the composition of the successive majorities on the Supreme Court holds out little hope for those that hope for a different line of reasoning to be applied, because it has not been the dynamic of a static block of justices narrowly ruling against the government, but of a broad consensus on the court that commercial speech is protected against blanket bans and prior restraint by a well understood and generation old test. The underlying mechanism of effective enforcement is the nature of FDA approval as a license to introduce into Interstate Commerce. Licenses can be subject to additional conditions, no provision in the FD&C as amended prevents additional restrictions on FDA Approval, and the agency could codify adherence to marketing practice as part of the terms of that license, just as disclosure is part of the terms of the patent process, and compulsory registration is part of the copyright process. While this does not apply to already approved medications, it could apply to future approvals.

Moreover, it would strengthen the Agency's position against future *Central Hudson* challenges, because it would cut to the standards that the court has applied in rejecting previous restrictions: there would be greater consistency in the government's scheme, it would not have a welter of exceptions, the government would be shown to be enforcing the underlying state interest, the restrictions would not be prior restraint, and the information provided would be at least potentially misleading. It would dispense with complex and unenforceable sets of guidelines.

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<sup>102</sup> *United States v. Sullivan*, 332 U.S. 689, 689 (1948).

Under the theory of damages presented in this paper, namely that sales of an improperly marketed drug impinge on the just expectations of complying with the license of FDA Approval, which qualifies as detrimental reliance, suits for improper marketing would have standing limited to those who can show damages. While this would open the door to class action suits on the part of patients, the class would have to show that but for the marketing, they would not have received the drug, which since the drug companies do not actually write the prescriptions, would be a difficult standard to meet. Instead the most common occurrence would be the ability of industry to enforce its own existing guidelines, by showing damages that occurred because of improper marketing. In this case a company would not have to show that a specific sale caused the damages, but merely that some part of the aggregate did.

### **Meeting Standards of Effective Regulation**

A tiered-labeling system provides all of the benefits of an efficient centralized regulatory scheme and an effective legal regime: uniformity, clarity, expertise, balance, and veracity. By having a system that predominately pulls with carrots, rather than pushes with sticks, but back-stopped with very powerful sticks (e.g., Medicare death penalty), the system generates voluntary incentives to engage in a cooperative Stag Hunt. The private entities will work closely with the government regulators to advance the public good, because it will also be in the best interest of the private party. The uniform flow of information to physicians through these clear and truthful indications of a drug's clinical profile, assured by the rigorous, comprehensive, unbiased expert review by the FDA, could improve the quality medical care, reduce medical errors, and avoid unnecessary healthcare spending.

## Uniformity

The uniform national standard avoids the inconsistency, complication, and confusion of having multiple state and local standards, prevents of “the race to the bottom” of defensive marketing and information overload. The new labeling scheme will be standardized nationally, so a patient from Nevada can show his medication list to his new physician in New York, who will be working with the same label that is communicating the same information as his Nevada physician did. With a uniform label, the physicians and the patient are all on the same page and collaborate with each without information barriers, without the need to consult different labels with local idiosyncrasies, and without the overly detailed label conforming to the most conservative standard.

While the state-law-based tort system, as reaffirmed by Wyeth, will still be in effect, a centrally administrated labeling system reduces any potential administrative costs of regulating different label should the state chose to do so, and the transactional costs of medical professionals trying to understand and adhere to different locality labels. Having a single clearinghouse for drug labeling will also ensure that the new system is closely integrated into the current regulatory scheme. Therefore, the tiered label has the virtue of uniformity: a system that is both practical and cost effective.

## Expertise

Closely connected to and setting the foundation for uniformity is the fact that the FDA, the foremost expert on drug regulation, will administer the program. Having both the science and medical expertise from regular approvals and a century-long history of regulating drug labeling,

the Agency is well equipped, perhaps with additional resources, from an institutional standpoint to carry out the task and ensure consistency with the approval labeling system. The regulatory and legal experience of agency with pharmaceutical marketing, and the working relationship with industry, will be useful in making sure that rules are properly followed and the system is not abused. The new labeling system's success rests on its accuracy, which the FDA's technical and regulatory expertise will more than adequately provide for.

### Veracity

One of the main purposes of the tiered labeling system is to accurately reflect the realities of medical practice and pharmaceutical use: the truth is physicians will always be prescribing drugs off-label. The gradations of the label match the nuance of our understanding of the drug's clinical effect. Many factors play into the amount of clinical research of a drug receives and the developmental status on an indication. The intermediate levels are both stepping stones toward full approval, and its exclusive benefits, and a label that truthfully indicates the drug's efficacy and safety. Additionally, physicians will be on-notice of drugs that are truly unapproved, without any of the intermediated designation.

Rather than engaging in prior restraint to try to eliminate off-label marketing, the system refocuses the efforts of pharmaceutical companies on conducting clinical research to find out more information on these yet-to-be approved indications. The pharmaceutical company, instead of being agents in crime of promoting off-label prescribing that is useless or even harmful to the patient, will be directed to uncover the drug's real clinical value. More informed medical decisions by physicians will undoubtedly improve patient care.

## Clarity

Improperly communicated information can be worse than the lack of information. Clarity is a major focus of the proposed system: the physicians and patients will not benefit much from quality discussed above, unless the format is one that is easy to understand and quickly accessible. The proposed system achieves clarity on both its design with intuitive levels and its presentation with color-coded summary box. The goal is to allow the physician to understand the system through a quick study and with the aid of nothing larger than a post card, and to access the information on the individual labels rapidly by glancing at the color coding. This innovation is superior to the current system where indications, clinical results, dosages are hidden within dense text and located in different parts of the label. The summary box will have the same prominence as a block box warning, except that the information it communicates is far more comprehensive and balanced.

## Balance

Ultimately, the proposed tiered labeling system is a critique of and a solution to the inability of current regulatory scheme to distinguish those off-label uses that are beneficial from those that are not. While part of the problem is the paradoxical hands-tied set-up of regulating off-label marketing without the authority to influence off-label use, a black and white labeling system with only the two levels of approval and non-approval does not have enough nuances to capture the information spectrum of clinical status. By providing a few shades of gray, the tiered label is not only a closer match to the reality, but also more importantly, presents a balanced view that advances of the public good of informed physicians and better quality healthcare for

patients.

The balanced approach is also fairer to the drug manufacturers, in that their efforts in advancing clinical understanding of the drugs, albeit not on the level of a full approval, will be reward and encouraged in a systemic manner under the supervision of the FDA. The current abuses of the system, ranging from blatant off-label marketing to fraudulent journal articles, will be greatly reduced when there are legal ways to improve the label without undergoing the full investment of approval. Therefore, the Prisoner's Dilemma will turn into a Stag Hunt for benefit of the public.

#### *Additional Benefits*

It is important to note several consequences that this approach does not promote. One is bounty hunting by outside or tangentially involved parties. The interest is in the license that the FDA issues, and therefore those who do not have an expectation of legal rights under such a license are not given any more grounds for action than present. The creation of rights often leads to those who attempt to purchase those rights and expand them, as is seen by "patent trolling," or the case of relator suits not based on original information. Under this system, the party that is damaged by an abuse of a license, and thus entitled to damages, is one who has a similar license and an expectation of its enforcement, or is a gatekeeper relying on the information provided. Patients, in the abstract, can already sue for malpractice if harmed, and under this theory of the license, absent that provable damage, would not gain additional cause of action.

Another important pitfall avoided is focusing on the process as adversarial. While enforcement mechanisms, from very broad to very specific, are contemplated here, the most

important pillar of the system is giving companies greater incentive to reveal positive information about their products, rather than on relators exposing allegedly negative information. The example of the study of GERD, acid reflux, is here important. The primary public interest is in the patients getting the best treatment, and bringing all parties that are part of the system into alignment to accomplish this. Enhancement, not enforcement, is promoted.

The third pitfall that is avoided is the pitfall of the combination of institutional timidity much of the time, combined with an incentive to institutional excess in spectacular cases. Companies with out clear financial incentive place drugs narrowly, only to "go for broke" with the blockbusters. The FDA has every incentive to launch high profile cases, but little incentive to improve the indication of smaller drugs. Congress has every incentive to step in at a moment of perceived crisis, and throw hundreds of pages of legislation forward, disregarding that key provisions are unlikely to survive established and broadly supported constitutional tests, but far less to provide a fair playing field.

## ***Conclusion***

In summary, the present regime for the regulation of off-label marketing does not promote the public's twin interests of availability and information. It does not improve access universally, with variability in how persuaded the physician is by the promotion and how payors handle the off-label status. It has clouded, rather than clarified information, by either skewing information in favor of the off-label use, or cloaking it in disrepute because of its off-label status. At the root of this is an adversarial set of systems which give participants strong incentives to risk adverse legal consequences, or to fail to take far smaller risks for far more sustainable

rewards, both motivated by institutional or personal gain. The proposed mechanism, by creating a tiered labeling system linked to clinical evidence, forces greater cooperation and increases incentives for research, in a design aimed at the public good, rather than at private profits and public recoveries in high profile cases. The systems will reduce current state of confusion, where there is little distinction between pharmaceutical sponsored biased literature and objective clinical research, and increased granularity provides greater clarity to physicians on the actual level of clinical evidence. More importantly, the tiered labeling system, unlike other blunt instruments of off-label enforcement, preserves the beneficial off-label prescribing, while eliminating those that are abusive and needlessly costing the public.