

# INCENTIVIZING PHARMACEUTICAL TESTING IN AN AGE OF OFF-LABEL PROMOTION

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*In 2012, the Second Circuit held that under the First Amendment, pharmaceutical manufacturers have a right to promote their drugs for uses for which they have neither been clinically tested nor FDA-approved. Weighing heavily in the Second Circuit's analysis was the argument that the FDA's prohibition on so-called "off-label speech" inhibited physicians' access to complete information, thereby harming public health. That line of reasoning has also created skepticism within Congress of the FDA's policy. Others argue that the prohibition on off-label speech is necessary in order to incentivize manufacturers to clinically test their drugs for all intended uses—a process that not only allows the FDA to certify the drug as safe and effective in each of its uses, but also creates a larger data set about a drug's effects before it begins to be marketed and prescribed. If manufacturers can market their pharmaceutical products for unapproved uses, they have reduced incentives to seek FDA approval, especially because the required clinical tests are extremely costly. Whatever one believes about a policy of permitting off-label promotion, it is clear that it not only creates benefits, but it also creates costs. This Note considers regulatory and common-law tools to reduce those costs. It rejects available regulatory tools, because either they are too weak to change manufacturers' incentives to conduct clinical tests, or they suffer from the same constitutional questions that troubled the Second Circuit. Instead, this Note argues that courts can hold manufacturers to a common-law duty to test their drugs for each use for which they market them, and it outlines what such a duty might entail. Such a solution, if properly implemented, would not only mitigate the concerns about the liberalization of off-label promotion, but it would also be supported by modern products liability doctrine.*

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## INTRODUCTION

Imagine the board rooms of two pharmaceutical companies. Let's call them Company A and Company B. Company A and Company B are identical in every respect, but they operate under different sets of legal rules. Both boards meet to make a decision about the preapproval testing to be conducted on a new experimental drug. Both boards believe that the drug might be prescribed to treat two different types of leukemia. Each board is considering whether to seek Food and Drug Administration (FDA) approval for both indications, or whether to test the drug's safety and effectiveness when used to treat just one of the two types. Both boards know that once the FDA approves a drug for one use, physicians can prescribe it for any use appropriate within their medical judgment. Company A, though, operates under laws that prohibit manufacturers from marketing their drugs for uses that have not been approved by the FDA. Company B operates under laws that permit manufacturers to market their drugs as treatments for unapproved uses, as long as their marketing is not misleading. Which board is more likely to choose to conduct expensive clinical trials for both indications?

Recent developments have moved the circumstances under which pharmaceutical manufacturers operate closer to those of Company B. In *United States v. Caronia*,<sup>1</sup> the Second Circuit held that the Federal Food, Drug and Cosmetics Act (FDCA) does not authorize the FDA to sanction pharmaceutical manufacturers or salesmen for marketing drugs for unapproved uses.<sup>2</sup> Interpreting the FDCA to prohibit unapproved (or "off-label") marketing, the Second Circuit held, would violate the First Amendment.<sup>3</sup> The court reached this conclusion in large part because it credited the policy arguments of those who advocate for allowing off-label marketing. Far from serving the government's interest in patient health, the Second Circuit reasoned, the prohibition on off-label marketing may harm that interest, as it disrupts manufacturers' ability to communicate data about their drugs to physicians, ultimately leaving physicians inadequately informed.<sup>4</sup> This argument

<sup>1</sup> 703 F.3d 149 (2d Cir. 2012).

<sup>2</sup> *Id.* at 162.

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

<sup>4</sup> *See id.* at 167 ("The government's construction of the FDCA essentially legalizes the outcome—off-label use—but prohibits the free flow of information that would inform that outcome.").

has persuaded both judges and legislators. Congress has pressed the FDA to change its policy on off-label promotion, and the 21st Century Cures Act,<sup>5</sup> passed in December 2016, explicitly allows manufacturers to promote off-label uses of their drugs to insurers.<sup>6</sup>

Whether or not one believes that permitting off-label promotion will ultimately result in better patient outcomes, it will also come with costs. Removing one of the most significant incentives to conduct tests for more than one indication—permission to market the drug for that indication<sup>7</sup>—will likely lead to reduced clinical testing.<sup>8</sup> When a new drug initially enters the market, then, although manufacturers might market drugs for more uses, physicians will have less information about the drug's safety and effectiveness for those uses. When physicians have less information, the quality of their treatment decisions suffer. Indeed, that is the very premise upon which proponents of off-label marketing base their argument. Changing the legal rules has essentially created a trade-off: Physicians will be provided with more real-world, post-approval patient data, but manufacturers will produce less clinical, preapproval data. Proponents of off-label promotion believe that the value of the added real-world patient data outweighs the value of the lost clinical data, and critics believe the reverse.

In this Note, I am the first to consider how to mitigate the costs of that tradeoff by using other means to incentivize manufacturers to test their drugs for each marketed use, finding that a duty to test in tort doctrine may be the best solution. In Part I, I set the terms of the debate on off-label promotion and describe its current state and trajectory. In Section I.A, I provide an overview of the approval process and the FDA's traditional prohibition of off-label marketing. In Section I.B, I discuss the Second Circuit's decision in *Caronia*, the momentum towards permitting off-label promotion, and the risks the trend creates. In Parts II and III, I consider various remaining options to incentivize manufacturers to conduct clinical testing for every intended use. In Part II, I examine various administrative solutions, but dismiss them because they would be ineffective, costly, or subject to the same legal challenges credited in *Caronia*. In Part III, I argue that state courts might incentivize manufacturers by embedding a duty

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<sup>5</sup> 21st Century Cures Act, Pub. L. No. 114-255 (2016).

<sup>6</sup> See *infra* note 81 and accompanying text.

<sup>7</sup> See *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 72 (D.D.C. 1998) (“[O]ne of the few mechanisms available to FDA to compel manufacturer behavior is to constrain their marketing options; i.e. control the labeling, advertising and marketing.”), *vacated in part*, *Wash. Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000).

<sup>8</sup> See *infra* notes 56–63 and accompanying text (discussing the high costs of clinical testing and the effect of the prohibition of off-label promotion on manufacturers' incentives to bear those costs).

to test within tort doctrine. Although courts have not required manufacturers to test their products for entirely unknown risks, such a standard would be consistent with basic tort principles.

## I

### ERODING INCENTIVES TO TEST

Pharmaceutical regulation in the United States is premised upon a preapproval regime. Only after a new drug is extensively tested and proven to be safe and effective for its intended uses will the Food and Drug Administration (FDA) grant it approval and permit it to be manufactured and sold. Clinical tests that allow the FDA to make such a judgment and provide doctors with data upon which they can make treatment decisions, however, are costly. In this section, I will discuss the incentives in place to ensure that manufacturers test their drugs' safety and effectiveness for each intended use—and how recent developments in the courts and the legislature have reduced those incentives. In Section I.A, I provide an overview of the FDA approval process and its importance, and describe how regulations have historically incentivized manufacturers to bear the costs of clinical tests. In Section I.B, I discuss recent developments that undermine those incentives and explain the harms that may result.

#### A. *The Path to FDA Approval*

As a matter of federal law, no pharmaceutical can be manufactured or sold in the United States unless the FDA has approved it to treat at least one disease or condition, or “indication.”<sup>9</sup> The FDA does not grant approval lightly. Before permitting the manufacture and sale of a new drug, the FDA requires significant data developed over several rounds of clinical testing.<sup>10</sup> The FDA confers approval only if its analysis of that data reveals that the drug may effectively be used for the indication for which the manufacturer seeks approval, that such use would be safe, and that the drug's benefits outweigh its risks.<sup>11</sup>

The application process is lengthy, expensive, and fraught with the risk of failure. Before manufacturers are permitted to administer a pharmaceutical to humans even in clinical trials, manufacturers must first successfully complete *in vitro* and animal testing.<sup>12</sup> If the results

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<sup>9</sup> 21 U.S.C. § 355(a) (2012).

<sup>10</sup> See *infra* notes 12–22 and accompanying text.

<sup>11</sup> See 21 U.S.C. § 355(d) (2012) (“The Secretary shall implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks . . .”).

<sup>12</sup> 21 C.F.R. § 312.23(a)(8) (2018) (requiring applications for permission to conduct clinical testing to include the results of *in vitro* and *in vivo* studies “on the basis of which

of those tests suggest that clinical trials would be reasonably safe, the FDA then permits the manufacturer to introduce the drug to humans on an investigatory basis.<sup>13</sup> Clinical trials proceed in three phases. At each phase, manufacturers routinely collaborate with the FDA to design accurate and useful studies, and also to define success by choosing target results.<sup>14</sup> The chosen endpoints, if met, must demonstrate that the drug is both safe and effective for the purposes for which the manufacturer seeks FDA approval.<sup>15</sup>

The clinical tests in Phase I are designed to reveal baseline information about the drug's safety.<sup>16</sup> To that end, the first phase of testing typically includes fewer than one hundred participants, all of whom are generally healthy.<sup>17</sup> By including only healthy participants, the studies generate preliminary information about the drug's metabolism, side effects, and general safety profile, while minimizing the risk of serious harm to the participants.<sup>18</sup>

Not until Phase II are clinical trials designed to measure the drug's effectiveness for particular uses.<sup>19</sup> Before beginning the second phase of clinical testing, therefore, manufacturers must determine the indications for which they will market the new drug. Phase II trials

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the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations”).

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

<sup>14</sup> See 1 JAMES T. O'REILLY & KATHARINE A. VAN TASSEL, FOOD & DRUG ADMINISTRATION § 13:8 (4th ed. 2018) (“The IND process includes meetings between the FDA staff reviewers and the drug developer before the products move into a second phase, the development of safety data from a small number of ill patients whose disease is the target of the particular new chemical.”).

<sup>15</sup> 21 C.F.R. § 314.105(c) (2018) (“FDA will approve [a new drug] after it determines that the drug meets the statutory standards for safety and effectiveness . . . .”); *id.* § 314.50(c)(2)(ii) (requiring applications for approval of new drugs to include the intended uses for which approval is sought).

<sup>16</sup> See 21 C.F.R. § 312.21(a)(1) (2018) (“[Phase 1] studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects of increasing doses, and, if possible, to gain early evidence on effectiveness.”).

<sup>17</sup> See *id.* (“Phase 1 studies . . . may be conducted in patients or normal volunteer subjects.”); 1 O'REILLY & VAN TASSEL, *supra* note 14, § 13:12 (“Phase I seeks pharmacologic effects information and early evidence on effectiveness in several dozen healthy persons.”).

<sup>18</sup> See 1 O'REILLY & VAN TASSEL, *supra* note 14, § 13:12; Rebecca Dresser, *First-in-Human Trial Participants: Not a Vulnerable Population, but Vulnerable Nonetheless*, 37 J.L. MED. & ETHICS 38, 41–42 (2009) (“In many cases, healthy people supply the ‘cleanest’ data, for it can be difficult to separate the effects of a study intervention from those caused by a patient’s disease or medications. . . . Healthy people can [also] ordinarily tolerate adverse effects from experimental interventions more easily than patients can.”). If the target of the drug exists only in individuals with a particular condition, however, then testing the drug on patients with that condition may better demonstrate its pharmacologic effects. *Id.* at 42 (describing how data from patients with the particular targeted condition will be more informative).

<sup>19</sup> 21 C.F.R. § 312.21(b).

include a few hundred participants who have the condition or disease that the drug will be used to treat.<sup>20</sup> These trials provide manufacturers and the FDA with early indicators of effectiveness, short-term side effects, and risks associated with intended uses.<sup>21</sup> The results of Phase II trials inform the design of Phase III testing, which expands trials to include several thousand participants and yields more complete data regarding the drug's safety risk and therapeutic benefits.<sup>22</sup> This data is critical to the FDA's decision whether or not to approve the drug for the indication tested. If the drug is ultimately approved, the data also forms the basis of the warnings and instructions on the drug's label.<sup>23</sup>

Altogether, from the time that a drug is created, it requires roughly ten to twelve years to obtain FDA approval.<sup>24</sup> It is not uncommon for pharmaceuticals to fail testing at any stage, and just 11.83% of new drugs are eventually approved.<sup>25</sup> The average cost associated with obtaining approval is roughly \$2.6 billion.<sup>26</sup>

Critically, the FDA does not approve drugs *generally*, but rather for particular indications.<sup>27</sup> Drugs, of course, present different risks and provide different benefits depending on the purposes for which they are used. A determination that a drug is safe and effective is necessarily contingent on what and whom it will treat.

First, a drug's safety profile may differ depending on the use to which it is put. Treating one condition may require a different dosage than another, and the mode of administration (e.g., pill, injection, intravenous) might also differ across indications.<sup>28</sup> Even if the mode

<sup>20</sup> *Id.*

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

<sup>22</sup> See *id.* § 312.21(c) (“[Phase 3 studies] are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects.”).

<sup>23</sup> *Id.*

<sup>24</sup> Merrill Matthews, *The High Cost of Inventing New Drugs – And of Not Inventing Them*, FORBES (Apr. 11, 2015, 8:00 AM), <http://www.forbes.com/sites/merrillmatthews/2015/04/11/the-high-cost-of-inventing-new-drugs-and-of-not-inventing-them/#7f497c667064>.

<sup>25</sup> Joseph A. DiMasi, Henry G. Grabowski & Ronald W. Hansen, *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. HEALTH ECON. 20, 23 (2016).

<sup>26</sup> *Id.* at 25 fig.2 (cost estimate includes out-of-pocket preclinical and clinical costs, cost of capital, and weighted risk of drug failure).

<sup>27</sup> See William S. Comanor & Jack Needleman, *The Law, Economics, and Medicine of Off-Label Prescribing*, 91 WASH. L. REV. 119, 120 (2016) (“Critically, drugs are approved only for the specific indications disclosed in the firm’s [application].”).

<sup>28</sup> See U.S. DEP’T OF HEALTH & HUMAN SERVS., FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION & RESEARCH, NONCLINICAL SAFETY EVALUATION OF REFORMULATED DRUG PRODUCTS AND PRODUCTS INTENDED FOR ADMINISTRATION BY AN ALTERNATE ROUTE: GUIDANCE FOR INDUSTRY AND REVIEW STAFF 4–9 (2015), <https://>

of administration is the same, if the location of administration is altered, different risks may be presented.<sup>29</sup> Patient populations suffering from different diseases also may respond differently to the same drug.<sup>30</sup> Moreover, patients with different diseases may be taking other medications simultaneously, and the new drug might interact adversely with those medications. A manufacturer cannot possibly test a drug's interaction with all other drugs, but it can test the drug's interaction with specific medications that many patients in the intended population likely take.<sup>31</sup>

Second, a drug's effectiveness will clearly differ depending on the condition or disease it is used to treat. A drug used to treat arrhythmia will likely not be as effective at treating kidney disease, or even at treating heart disease generally. A drug's effectiveness is just as critical as its safety. A patient who forgoes an effective treatment to take an ineffective treatment bears an opportunity cost equal to the benefits that the effective treatment would provide. Imagine there are two drugs that purport to treat heart disease. One reduces the risk of heart attack by 20% and the other does not reduce the risk of heart attack at all. Those who take the ineffective medication bear a cost—a 25%

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[www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079245.pdf](http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079245.pdf) (discussing recommended toxicity tests, which vary by route of administration).

<sup>29</sup> For instance, Depo-Medrol was a corticosteroid solution approved to treat various types of inflammation. The FDA had approved Depo-Medrol for injections in muscles, joints, and lesions, because each had good blood supply. Not long after Depo-Medrol was first introduced to the market, several ophthalmologists communicated to the manufacturer that they wanted to use Depo-Medrol to treat certain ophthalmic conditions, which would require injections near the eye. The manufacturer supplied Depo-Medrol to the ophthalmologists, telling them that there had been no reports concerning that use, and they were interested to see the results. *See Proctor v. Davis*, 291 Ill. App. 3d 265, 268–70 (1997). One risk of injection *around* the eye is accidental injection *in* the eye, which would have catastrophic consequences, including blindness. *Id.* at 276.

<sup>30</sup> For example, patients suffering from acute post-operative pain have different vulnerabilities than patients suffering from chronic pain. The FDA had approved fentanyl patches to treat chronic pain but not acute post-operative pain for fear that it might cause respiratory depression, or hypoventilation. Because some publications had suggested that fentanyl patches were safe and effective for post-operative pain, several physicians prescribed them for that use. Sure enough, many patients suffered from life-threatening respiratory depression. Linda A. Suydam, Senior Assoc. Comm'r, Food & Drug Admin., Address at the FDLI Conference on Advertising and Promotion in the New Millennium (Sept. 13, 1999), <http://www.fda.gov/NewsEvents/Speeches/ucm054540.htm>.

<sup>31</sup> *Cf.* Lars Noah, *This Is Your Products Liability Restatement on Drugs*, 74 BROOK. L. REV. 839, 908 (2009) (“Obviously, if a manufacturer discovers a dangerous interaction during clinical trials or postmarket surveillance, then it would have a duty to communicate information about the risk.”). Even if manufacturers do not test *for* adverse interactions with other drugs, they are more likely to discover the most relevant of such interactions in the course of testing if they test them in the populations of patients that they intend to treat.

greater risk of heart attack<sup>32</sup>—compared to those who take the effective medication. This cost is no less real than those borne by patients who take a new medication that purports to treat a previously incurable condition but in fact increases the risk of heart attack by 25%. Effectiveness is a close cousin of safety.

Finally, the FDA must ensure that a drug's benefits outweigh its risks. If a drug effectively treats life-threatening diseases, the FDA is more tolerant of significant safety risks. But if a drug's side effects or risks are more significant than the improvement in the treated condition, it is not worth taking. Because safety and effectiveness both vary by use, the FDA needs data on both the drug's safety and effectiveness for each indication.

Historically, the FDA has effectively, albeit indirectly, prohibited pharmaceutical manufacturers from marketing their drugs for uses for which they have not been approved. The Federal Food, Drug & Cosmetic Act (FDCA) prohibits "misbranding,"<sup>33</sup> and it states that a drug is misbranded if, *inter alia*, its labeling does not contain "adequate directions for use."<sup>34</sup> The FDA, in turn, interprets "adequate directions for use" to require the drug's label to state the uses for which the drug is intended<sup>35</sup> and instructions for how to safely use the drug for those uses.<sup>36</sup> Finally, to determine a drug's "intended uses," the FDA looks to the uses for which the manufacturer promotes it: Promotion serves as evidence of intent. Because the label contains information about only FDA-approved uses, when a manufacturer promotes a drug for an unapproved use, the drug is considered misbranded.

The FDCA, however, regulates only the manufacture and sale of pharmaceuticals: It emphatically does not regulate the practice of medicine.<sup>37</sup> Therefore, although manufacturers may not promote

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<sup>32</sup> Assume that one out of every ten people who takes the ineffective medication suffers from a heart attack, so each person bears a 0.1 risk. Only eight out of every one hundred people who take the effective medication suffer from a heart attack, a 0.08 risk. Because  $0.1 = 1.25 \times 0.08$ , those who take the ineffective medication have a 25% greater risk of heart attack.

<sup>33</sup> 21 U.S.C. § 331(b) (2012).

<sup>34</sup> *Id.* § 352(f).

<sup>35</sup> 21 C.F.R. § 201.5(a) (2018).

<sup>36</sup> *See id.* § 201.5(b) (requiring statements to provide the recommended dose for each of the uses for which it is intended based on age and physical condition).

<sup>37</sup> *See* 21 U.S.C. § 396 (2012) ("Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship."); James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 *FOOD & DRUG L.J.* 71, 76 (1998) ("FDA never has had authority to regulate the practice of

drugs for off-label uses, physicians are not prohibited from prescribing them for such indications.<sup>38</sup> Indeed, off-label prescription is common and is even critical to certain specialties.<sup>39</sup> Although federal law preserves physicians' power to prescribe, the scope of a physician's discretion is not unlimited: It can be challenged in malpractice or negligence actions, and physicians are also subject to professional censure.<sup>40</sup>

The net result is somewhat odd. Physicians may prescribe drugs for unapproved indications, but manufacturers are not permitted to provide physicians with information about their drugs' safety or effectiveness for those indications. Although manufacturers are arguably best positioned to aggregate and distribute information about off-label uses, physicians instead are forced to rely on other sources, such as studies published in medical journals, for information.<sup>41</sup> Many have argued that, as a result, physicians lack the best information about the drugs they prescribe, thereby impeding their ability to make the best decisions for their patients.<sup>42</sup>

### B. *Caronia and the Liberalization of Off-Label Speech*

The Second Circuit confronted this paradox head-on in *United States v. Caronia*. A pharmaceutical salesman had been prosecuted for promoting a drug for unapproved uses, and he was convicted of crim-

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medicine; physicians may use legally marketed drugs or devices in any way that they believe, in their professional judgment, will best serve their patients.”).

<sup>38</sup> See Beck & Azari, *supra* note 37, at 76; 2 O'REILLY & VAN TASSEL, *supra* note 14, § 15:65 (“The individual physician is free to prescribe drugs for an off-label use . . .”).

<sup>39</sup> One study found that roughly one-fifth of all prescriptions are off-label. David C. Radley et al., *Off-Label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1023 (2006). And off-label uses are especially important in some fields, such as oncology. See Rebecca Dresser & Joel Frader, *Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, 37 J.L. MED. & ETHICS 476, 476 (2009) (“In oncology, pediatrics, geriatrics, obstetrics, and other practice areas, patient care could not proceed without off-label prescribing.”).

<sup>40</sup> See *United States v. Caronia*, 703 F.3d 149, 168 n.11 (2d Cir. 2012) (stating that physicians “can be held accountable for off-label drug use through malpractice and negligence theories of liability”); Proposed New Drug, Antibiotic, and Biologic Drug Product Regulations, 48 Fed. Reg. 26,720, 26,733 (June 9, 1983) (“The primary legal constraints [on off-label prescription] are State laws on medical practice and products liability law.”).

<sup>41</sup> Unlike manufacturers, physicians, and researchers—anybody other than a drug's manufacturer—are permitted to discuss or even encourage off-label uses. *Caronia*, 703 F.3d at 165.

<sup>42</sup> See, e.g., Coleen Klasmeyer & Martin H. Redish, *Off-Label Prescription Advertising, the FDA and the First Amendment: A Study in the Values of Commercial Speech Protection*, 37 AM. J.L. & MED. 315, 347 (2011) (“[S]hould we want prescribing doctors to be made fully aware of valuable off-label uses? The answer most assuredly must be yes; . . . Yet the FDA's categorical ban on manufacturer promotion will likely have this impact.”).

inal misbranding.<sup>43</sup> On appeal, the salesman argued that the FDA's effective prohibition of off-label marketing unconstitutionally restricted speech in violation of the First Amendment.<sup>44</sup>

The Second Circuit agreed with the salesman and held that his conviction could not withstand the standard of intermediate scrutiny that *Central Hudson Gas & Electric Corp. v. Public Service Commission*<sup>45</sup> mandates upon review of restrictions on non-misleading commercial speech.<sup>46</sup> Under *Central Hudson*, a restriction on non-misleading commercial speech is constitutional only if (i) the asserted public interest is substantial; (ii) the regulation directly advances that interest; and (iii) the regulation is not over-restrictive but is instead "narrowly drawn" to that interest.<sup>47</sup>

Although the Second Circuit credited the FDA's asserted substantial interests in "drug safety and public health" generally and "in preserving the effectiveness and integrity of the FDCA's drug approval process" and in "reducing patient exposure to unsafe and ineffective drugs" specifically,<sup>48</sup> it held that the effective prohibition of off-label marketing did not directly advance those interests and in any event was substantially more restrictive than the First Amendment permits.<sup>49</sup> The court's opinion was driven in large part by its concern with the paradox effected by the FDA's policy: Physicians legally could and routinely did prescribe drugs for unapproved uses, but manufacturers were unable to provide them with information that would enable them to make better choices. The Second Circuit feared that, far from furthering the government's interest in drug safety, the FDA's policy actually jeopardized patients' safety by interfering with the flow of information to physicians.<sup>50</sup> The FDA's restriction therefore failed *Central Hudson*: It did not directly advance any substantial interest.<sup>51</sup>

Many have noted weaknesses in *Caronia*'s constitutional analysis. Some have argued that the First Amendment was not germane because the FDA regulates conduct, not speech.<sup>52</sup> They argue that the

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<sup>43</sup> *Caronia*, 703 F.3d at 155–60.

<sup>44</sup> *Id.* at 160.

<sup>45</sup> 447 U.S. 557 (1980) (sustaining a constitutional challenge to regulation prohibiting utility companies from promoting usage of electricity).

<sup>46</sup> *Id.* at 566.

<sup>47</sup> *Id.* at 565–66.

<sup>48</sup> *Caronia*, 703 F.3d at 166.

<sup>49</sup> *Id.* at 166–69.

<sup>50</sup> *Id.* at 167–68.

<sup>51</sup> See *supra* notes 45–47 and accompanying text.

<sup>52</sup> See, e.g., Christopher Robertson, *The Tip of the Iceberg: A First Amendment Right to Promote Drugs Off-Label*, 78 OHIO ST. L.J. 1019, 1031–35 (2017).

FDA directly polices the content of drug labels, and that manufacturers' speech is merely evidence of intent, which bears on the adequacy of the drug label.<sup>53</sup> Although this may be a formal distinction, *Caronia's* holding is arguably inconsistent with the law's acceptance of speech as evidence of intent in several other contexts.<sup>54</sup> Even if one accepts that the FDA regulates speech, others have argued that *Central Hudson* should provide no protection because off-label speech is inherently misleading. Specifically, without clinical data and FDA approval, the validity of claims about a drug's safety and effectiveness is necessarily uncertain.<sup>55</sup>

Most importantly for the purposes of this Note, however, several scholars have argued that the Second Circuit erred in its application of the *Central Hudson* test because it fundamentally misunderstood the manner in which the prohibition of off-label marketing supports the government interest in health and safety. Those critics argue that the prohibition powerfully incentivizes manufacturers to conduct clinical testing of and seek approval for more than just a single indication.<sup>56</sup> Clinical trials reveal important information about the safety and effectiveness with which a drug treats a disease or condition,<sup>57</sup> information upon which physicians can confidently rely when making prescription decisions, but they are costly.<sup>58</sup> The average out-of-pocket costs associated with Phases II and III—the indication-specific stages of clinical trials—are \$58.6 million and \$255.4 million, respectively.<sup>59</sup> Moreover, if a drug fails clinical trials for a particular indication, physicians may be less likely to prescribe the drug than if it had never been tested for

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<sup>53</sup> *Id.*

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

<sup>55</sup> See, e.g., Stephanie M. Greene, *After Caronia: First Amendment Concerns in Off-Label Promotion*, 51 SAN DIEGO L. REV. 645, 690–700 (2014) (noting that prohibition of off-label promotion ensures that drugs are first properly tested); Henry A. Waxman, *A History of Adverse Drug Experiences: Congress Had Ample Evidence to Support Restrictions on the Promotion of Prescription Drugs*, 58 FOOD & DRUG L.J. 299, 306–10 (2003) (stating that without FDA testing requirements, it is difficult for doctors to know which products are effective for different conditions).

<sup>56</sup> See generally Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 370 (2007) (explaining that because the FDA requires that “firms conduct rigorous clinical trials before bringing their products to market and before making promotional claims . . . the FDA plays an important structural role in promoting a valuable form of biomedical R&D [research and development] that private firms are undermotivated to perform . . . while internalizing the costs of this R&D to the firms”).

<sup>57</sup> See *supra* Section I.A (discussing testing process and its utility).

<sup>58</sup> See *supra* notes 24–26 and accompanying text (discussing high cost of clinical trials).

<sup>59</sup> Comanor & Needleman, *supra* note 27, at 135.

that indication at all.<sup>60</sup> And failure is common: 44% of drugs fail Phase II trials, and more than 10% fail Phase III trials.<sup>61</sup>

If a manufacturer could take advantage of the market for a treatment of a particular condition or disease without bearing such significant cost and risk, it is reasonable to believe that at least some, and perhaps most, would. Because physicians can legally prescribe off label, the only barrier to such a scenario was the FDA's restriction on manufacturers' ability to market their drugs.<sup>62</sup> *Caronia* removes that barrier. It risks incentivizing manufacturers to seek approval only for one indication, not several, and perhaps even only for the indication about which the manufacturer is most confident it will be successful.<sup>63</sup> As a result, when a drug first reaches the market, physicians, who can rely on clinical data when making prescription decisions, may initially have less clinical data upon which to base their decisions, although they will likely have better access to real-world patient data gathered in the years after patients are first treated. In a sense, the *Caronia* decision reflects the court's preference for the communication of real-world patient data, rather than the preapproval generation of data from clinical trials.

The Second Circuit considered these arguments, but it did not credit them. Instead, it focused on the existence of alternative mechanisms to advance the government's interest. Some, such as requiring a disclaimer that the drug is not approved for the particular use,<sup>64</sup> would provide a far weaker incentive to test, especially because physicians routinely prescribe drugs off label. Others, such as prohibiting or imposing a ceiling on off-label prescriptions, would unduly infringe on physicians' ability to prescribe off label,<sup>65</sup> which even the FDA recognizes can be beneficial under the appropriate circumstances.<sup>66</sup> Such circumstances include, for instance, situations in which a patient with

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<sup>60</sup> Cf. Rebecca S. Eisenberg, *The Problem of New Uses*, 5 YALE HEALTH POL'Y L. & ETHICS 717, 718 (2005) ("From the perspective of a firm that has a lucrative pharmaceutical product on the market rigorous clinical trials of new indications present a risk of generating results that could destroy the value of the product rather than enhance it.").

<sup>61</sup> Comanor & Needleman, *supra* note 27, at 135.

<sup>62</sup> See *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 72 (D.D.C. 1998) ("[O]ne of the few mechanisms available to FDA to compel manufacturer behavior is to constrain their marketing options; i.e. control the labeling, advertising, and marketing.").

<sup>63</sup> See *United States v. Caronia*, 703 F.3d 149, 178 (2d Cir. 2012) (Livingston, J., dissenting) ("If drug manufacturers were allowed to permit FDA-approved drugs for non-approved uses, they would have little incentive to seek FDA approval for those uses.").

<sup>64</sup> *Caronia*, 703 F.3d at 168.

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

<sup>66</sup> See *Use of Approved Drugs for Unapproved Indications*, 12 FDA DRUG BULLETIN 4-5 (1982) ("'[U]napproved' or more precisely 'unlabeled' uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that

a dire condition has not improved while taking approved treatments, or, because the FDA considers statistically average patients when approving new drugs, situations in which patients have peculiar attributes.<sup>67</sup> This alternative, therefore, would come at too high a cost to the very interest that the FDA seeks to protect.<sup>68</sup>

Regardless, the Second Circuit's position will likely carry the day in the courts and perhaps even at the FDA, which did not seek certiorari in *Caronia*.<sup>69</sup> Commentators speculated that this was a strategic decision not to risk elevating the Second Circuit's analysis and holding to Supreme Court precedent.<sup>70</sup> This decision could cut both ways: On one hand, the choice may reflect the FDA's lack of confidence in the constitutionality of its effective prohibition of off-label promotion. On the other hand, it may demonstrate the FDA's intention to resist similar holdings in other circuits.<sup>71</sup> Shortly after the *Caronia* decision was announced, the FDA announced that it would not "significantly affect the agency's enforcement of the drug misbranding" under the FDCA.<sup>72</sup>

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have been extensively reported in medical literature . . . ."), cited in 59 Fed. Reg. 59,820, 59,821 (Nov. 18, 1994).

<sup>67</sup> See Richard A. Epstein, *Against Permittitis: Why Voluntary Organizations Should Regulate the Use of Cancer Drugs*, 94 MINN. L. REV. 1, 37 (2009) ("The FDA . . . ignores the variations of patient responses by basing its decision on average responses. This approach tends to deny licensing approvals to products that serve a fraction of the overall population, even if it is of no benefit to the rest."); Comanor & Needleman, *supra* note 27, at 137 ("While clinical trials estimate average effects, one of the hallmarks of drug therapies is the heterogeneity of patient outcomes . . . . Physicians need to tailor their choices of therapy to the responsiveness of their patients."). Off-label prescribing is especially prevalent when clinical trials are for one reason or another difficult to complete. See *id.* at 137 (noting this to be the case when treating children, because it is often rare for a disease or condition to affect young people).

<sup>68</sup> See also *Caronia*, 703 F.3d at 179–80 (Livingston, J., dissenting) ("A ceiling on off-label prescriptions . . . could needlessly (and simultaneously) result in the denial of some effective treatments and the over-prescription of ineffective and even dangerous ones. . . . [A] ban on off-label prescriptions would be no better.").

<sup>69</sup> See Thomas M. Burton, *FDA Won't Appeal Free-Speech Marketing Decision*, WALL ST. J. (Jan. 23, 2013, 8:20 PM), <http://www.wsj.com/articles/SB10001424127887324539304578260323575925896>.

<sup>70</sup> See, e.g., Thea Cohen, *The First Amendment and the Regulation of Pharmaceutical Marketing: Challenges to the Constitutionality of the FDA's Interpretation of the Food, Drug, and Cosmetics Act*, 49 AM. CRIM. L. REV. 1945, 1946–47 (2012) (arguing that the Supreme Court would likely hold the FDA's regulatory scheme unconstitutional); John C. Richter & Daniel C. Sale, *The Future of Off-Label Promotion Enforcement in the Wake of Caronia — Toward a First Amendment Safe Harbor*, 14 SEDONA CONF. J. 19, 31 & n.86 (2013) (arguing that the FDA made a calculated choice not to appeal because the Supreme Court was likely to embrace the Second Circuit's reasoning); Burton, *supra* note 69.

<sup>71</sup> See Burton, *supra* note 69 (quoting the speculation of an attorney, who did not work on the case, that the FDA "may have . . . decided they're better off trying to get around" the Second Circuit's holding than challenging it directly in the Supreme Court).

<sup>72</sup> *Id.*

Commentators were skeptical of this announcement. Many predicted that the FDA would choose to focus on false and misleading marketing,<sup>73</sup> as the agency may prefer to allocate its scarce resources to enforcement actions that rest on more secure constitutional footing. Others predicted that the FDA would focus on enforcement of anti-kickback statutes.<sup>74</sup> The likelihood that the FDA would deemphasize enforcement of the ban on off-label promotion only increased when, in *Amarin Pharma, Inc. v. FDA*,<sup>75</sup> the court refused to limit *Caronia*'s holding to its own facts.<sup>76</sup> Since *Caronia*, the FDA has brought a few enforcement actions against manufacturers for off-label promotion, but it has been forced to accept far lower settlements when the promotion is not false or misleading—a clear recognition of the Second Circuit decision.<sup>77</sup>

Even if the FDA does not change its position on off-label promotion, it may be overridden by the courts or by Congress. In an era of expanding and deregulatory First Amendment doctrine,<sup>78</sup> courts may find it easy to follow the Second Circuit's analysis in *Caronia*. Congress, too, has signaled that it would prefer off-label promotion be permitted in some form or another. In May of 2016, the Chairman of

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<sup>73</sup> See Richter & Sale, *supra* note 70, at 31 (“[E]ven if the government does not fully embrace the [*Caronia*] opinion, it is likely to shift its focus to enforcement of only false or misleading promotional statements . . . .”); Kellie Combs & Albert Cacoza, *Drug Promotion in the Post-Caronia World*, FOOD & DRUG L. INST. UPDATE MAG. 15, March/April 2013, at 14, 15 (“The FDA may begin to focus its enforcement efforts on instances where a manufacturer’s speech is not only inconsistent with the approved product label, but is also false or misleading in violation of the FDCA.”).

<sup>74</sup> See David Kirman & Alexander Wyman, *Anti-Kickback Statute Enforcement Trends*, HEALTH L., Dec. 2015, at 43, 45 (speculating that enforcement of the Anti-Kickback Statute may increase because “the government and relators’ bar are facing headwinds in off-label cases . . . and investigative resources may be shifted to bringing cases with less legal uncertainty”).

<sup>75</sup> 119 F. Supp. 3d 196 (S.D.N.Y. 2015).

<sup>76</sup> There had been some question whether *Caronia* would be applied outside the context of a *criminal* conviction in which jury instructions indicated that evidence of off-label promotion would be sufficient to convict. See *Amarin*, 119 F. Supp. 3d at 223–24 (“The FDA . . . views *Caronia* as a fact-bound decision that turned on the particular jury instructions and government jury addresses given in *Caronia*’s trial.”). The court in *Amarin* squarely rejected such an argument. *Id.* at 226 (“This Court therefore rejects the FDA’s reading of *Caronia* as a mere artifact of that case’s particular facts and circumstances.”).

<sup>77</sup> See Richter & Sale, *supra* note 70, at 31–34. For instance, the Department of Justice was able to secure a massive \$762 million settlement with Amgen, Inc., which engaged in a concerted effort to promote its drug Aranesp for unapproved uses, including by using some false statements. In contrast, the FDA could secure only a \$45 million settlement with Par Pharmaceuticals, which was not alleged to have made false or misleading statements. See *id.* at 31–33.

<sup>78</sup> See Amanda Shanor, *First Amendment Coverage*, 93 N.Y.U. L. REV. 318, 322 (2018) (“The First Amendment’s borders are now in a period of grand transformation—largely expansion, and rapid, at that.”). See generally Amanda Shanor, *The New Lochner*, 2016 WIS. L. REV. 133 (2016) (describing expansion of the First Amendment).

the House Committee on Energy and Commerce and the Chairman of its Subcommittee on Health wrote a letter to Sylvia Burwell, Secretary of the Department of Health and Human Services, urging a change in FDA policy allowing manufacturers to convey to physicians more information about off-label uses.<sup>79</sup> The letter emphasizes that physician access to accurate, up-to-date scientific information about *all* of a drug's uses is "critical to optimizing patient care," and it calls attention to the litigation undermining the FDA's constitutional authority to restrict off-label communication.<sup>80</sup> In December of 2016, Congress passed the landmark 21st Century Cures Act, which, among other things, permits pharmaceutical companies to promote off-label uses to insurance companies.<sup>81</sup>

In the next section, I consider possible strategies to mitigate the risks posed by permitting off-label promotion. Taking as a given the adoption of *Caronia*'s analysis, how might the FDA and the courts maintain manufacturers' incentives to test their drugs for each marketed use? Stated another way, must we, as a practical matter, choose between the free flow of real-world patient data and the generation of clinical data, and what legal rules might encourage both?

## II

### REGULATORY INCENTIVES TO TEST

The previous section described the risks associated with off-label marketing, risks that may be imminent in the wake of the Second Circuit's decision in *Caronia*. Specifically, if manufacturers are permitted to market their drugs for off-label uses, they may be incentivized to conduct less clinical testing.<sup>82</sup> Before *Caronia*, the benefits that flow from marketing a drug for an indication incentivized manufacturers to undertake the substantial costs and risks of seeking FDA approval. By giving manufacturers the constitutional right to market drugs for unapproved indications, *Caronia* removes a strong incentive

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<sup>79</sup> Letter from Fred Upton, Chairman of the House Comm. on Energy and Commerce, and Joseph R. Pitts, Chairman of the Subcomm. on Health, to Sylvia Burwell, Sec'y of the Dep't of Health and Human Servs. (May 26, 2016), <https://energycommerce.house.gov/sites/republicans.energycommerce.house.gov/files/documents/114/letters/20160526HHS.pdf>.

<sup>80</sup> *Id.*

<sup>81</sup> See Sheila Kaplan, *Winners and Losers of the 21st Century Cures Act*, STATNEWS (Dec. 5, 2016), [https://www.statnews.com/2016/12/05/21st-century-cures-act-winners-losers/?s\\_campaign=FB&utm\\_content=Buffer42708&utm\\_medium=social&utm\\_source=facebook.com&utm\\_campaign=buffer](https://www.statnews.com/2016/12/05/21st-century-cures-act-winners-losers/?s_campaign=FB&utm_content=Buffer42708&utm_medium=social&utm_source=facebook.com&utm_campaign=buffer).

<sup>82</sup> See Eisenberg, *supra* note 56, at 369–71 ("The control mechanisms that the FDA uses—setting barriers to bringing new products to market and limiting permissible promotional claims—make more sense as a way of motivating firms to conduct rigorous trials than as a way of protecting patients from risks of harm.")

to seek approval for more than one indication, the bare minimum required before a drug can be manufactured and sold. Clinical data about a drug's safety and effectiveness for various indications is a public good<sup>83</sup>: Physicians can rely on clinical data when making prescription decisions. If pharmaceutical manufacturers conduct fewer clinical tests, then physicians will have less data to guide their decision making, and they will therefore make treatment decisions under conditions of greater uncertainty. Although physicians may be aware of more real-world data, that is no replacement for data produced in scientifically designed tests. The problem is especially acute before real-world results reach a significant sample size and are thoroughly analyzed: a process which likely takes years or even decades.

Whether or not one believes that the gains in the communication of real-world patient data wrought by liberalizing off-label promotion outweigh the risk of disincentivizing clinical trials, most would agree that the optimal scenario is for physicians to have access both to sufficient real-world and clinical patient data. In this section, I consider potential administrative and judicial solutions that may mitigate the risk posed by manufacturers' reduced incentive to conduct additional clinical trials. In this Part, I consider various administrative solutions but ultimately dismiss them as ineffective, costly, or plagued by constitutional problems similar to those addressed in *Caronia*. It is important to note at the outset that the 21st Century Cures Act, which expressly permits manufacturers to promote their drugs to *insurers* for off-label uses,<sup>84</sup> would not deprive the FDA of whatever statutory power they have to prevent manufacturers from promoting their drugs to *doctors* for those uses.

At first glance, it might seem that the FDA is better equipped to impose incentives to test than are common-law courts. The FDA, after all, has far greater expertise in the pharmaceutical field than do courts and judges. Because the FDA has significant experience with countless conditions and families of drugs as well as with designing trials to reveal drugs' properties, the FDA might be better able to more effectively tailor incentives. Moreover, the FDA could promulgate testing protocols or other requirements with greater specificity than can courts. The common law often rests on standards, whereas the FDA could act quasi-legislatively and promulgate incentive-creating rules with precision. Unlike private litigants, the FDA could also act proactively, avoiding the obstacles to private enforcement such as the high costs of private litigation or the requirement of proof of loss causa-

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<sup>83</sup> See *id.* at 370.

<sup>84</sup> See *supra* note 81 and accompanying text.

tion. Moreover, rather than relying on private parties to hold manufacturers accountable once harm materializes, *ex ante* regulation would allow the FDA to sanction behavior that risks injury before it occurs.<sup>85</sup>

Although these considerations are informative, they are ultimately abstractions. It is critical not only to examine the relative advantages of individual actors, but also to consider the merits of the specific policies that each might adopt.

Those who have advocated lifting restrictions on off-label speech often make a simple proposal: require disclosures that the use has not been FDA-approved.<sup>86</sup> But such a requirement would do little to nothing to address the risks posed by off-label speech. It would not, of course, require manufacturers to conduct any testing before promoting their drugs for a particular use. Nor would it provide more than a trivial incentive to perform such testing.<sup>87</sup> It is hard to imagine that the cost of complying with a disclosure requirement would be significant enough even to be a consideration for manufacturers choosing between pursuing FDA approval for a particular use or simply promoting the drug off label. And the cost of obtaining FDA approval<sup>88</sup> surely outweighs any marketing advantage that would be achieved by removing the disclosure. Simply put, a disclosure requirement would likely do little to increase drug testing for off-label uses.

Alternatively, as the *Caronia* court suggested, manufacturers would be incentivized to test drugs for additional indications either if it were illegal for physicians to prescribe drugs for unapproved uses or if there were a cap on such prescriptions.<sup>89</sup> But imposing those regula-

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<sup>85</sup> See Richard A. Posner, *Regulation (Agencies) Versus Litigation (Courts): An Analytical Framework*, in *REGULATION VERSUS LITIGATION: PERSPECTIVES FROM ECONOMICS AND LAW* 16 (Daniel P. Kessler ed., 2011) (“Since [litigation] is unlikely to be 100 percent effective, *ex ante* regulation is strongly indicated when the regulated activity can give rise to catastrophic injury. The greater the injury if deterrence fails and the likelier deterrence is to fail, the stronger the case for *ex ante* regulation.”).

<sup>86</sup> See, e.g., *United States v. Caronia*, 703 F.3d 149, 168 (2d Cir. 2012) (“The government could develop its warning or disclaimer systems . . . .”); *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 73 (D.D.C. 1998) (“Full disclosure not only addresses all of the concerns advanced by the FDA, but addresses them more effectively.”).

<sup>87</sup> See Brief for the Government at 71, *Caronia*, 703 F.3d 149, No. 09-5006-cr(L), 10-0750(CON), 2010 WL 6351497, at \*71 (“Allowing drug manufacturers to promote drugs for off-label uses as long as they disclose that the uses are not FDA-approved . . . would radically undermine the incentives for manufacturers to go through the new drug approval process.”).

<sup>88</sup> Roughly \$2.6 billion including the cost of capital and the risk of failure. See *supra* note 26 and accompanying text.

<sup>89</sup> See *Caronia*, 703 F.3d at 168 (“To minimize off-label use, or manufacturer evasion of the approval process for such use, the government could create other limits, including

tions would amount to a dramatic expansion of federal control over the practice of medicine, a matter typically left to state regulation. Moreover, off-label prescription is not necessarily harmful: Even the FDA recognizes that it can be an important tool for physicians.<sup>90</sup> Because FDA approval is premised upon average patient responses, a drug may treat some patient groups more effectively or safely than others. If a physician identifies a patient as belonging to a particular population, she might reasonably believe that an off-label use is the most effective option, even though it has not been approved by the FDA. Moreover, many diseases or conditions appear so infrequently in particular populations that bearing the cost of approval is not economical, and so doctors must prescribe off label. It is especially common, for instance, for drugs not to be approved to treat children.<sup>91</sup> The harm to be avoided is not caused by physician behavior, but rather by the behavior of manufacturers. This option would come at too great a cost and is aimed at the wrong target.

Finally, the FDA might act more aggressively and impose specific testing standards that must be met before manufacturers may promote their drugs. The FDA might model these testing standards on the requirements it imposes on claims of a drug's superiority in advertising. Manufacturers making claims with respect to safety or effectiveness must support their statements with "substantial evidence."<sup>92</sup> Such "substantial evidence" must consist of "adequate and well-controlled investigations," including clinical testing in humans, conducted by experts, on the basis of which experts would conclude the claim is true.<sup>93</sup> Typically, at least two trials are required in order to determine

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ceilings or caps on off-label prescriptions. . . . [W]here off-label drug use is exceptionally concerning, the government could prohibit the off-label use altogether."

<sup>90</sup> See Suydam, *supra* note 30; Klasmeyer & Redish, *supra* note 42, at 316.

<sup>91</sup> See Comanor & Needleman, *supra* note 27, at 126.

<sup>92</sup> 21 C.F.R. § 202.1(e)(6)(ii). This provision also states that comparative claims can be supported by "substantial clinical experience," but typically the FDA does not permit claims based only on clinical experience. See Bethany Fox, *Closing the Information Gap: Informing Better Medical Decisionmaking Through the Use of Post-Market Safety and Comparative Effectiveness Information*, 67 *FOOD & DRUG L.J.* 83, 97 (2012) ("Practically speaking, substantial clinical experience isn't a standard used by FDA to permit effectiveness claims that fail the substantial evidence standard."); see also U.S. Dep't of Health & Human Servs., Warning Letter to Joseph Pieroni, CEO of Sankyo Pharma, Inc., Jan. 6, 2006 (stating that, in general, comparative effectiveness claims should meet the standard for substantial evidence), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/ucm054388.pdf> [<https://web.archive.org/web/20110819035011/http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/ucm054388.pdf>].

<sup>93</sup> 21 C.F.R. § 202.1(e)(4)(ii)(b).

that the results are replicable.<sup>94</sup> Requiring similar testing before marketing a drug for an off-label use could be called a kind of “approval-lite.” The result would be a kind of two-tier approval system.

This kind of regulation has obvious advantages. First, it would provide clear guidance to manufacturers and reduce much of the uncertainty that deregulation of off-label speech might create.<sup>95</sup> Second, it would ensure that there is some body of data that physicians can consult before prescribing a medication for a particular indication. In essence, the advantages of this option mirror the advantages of the FDA’s historical reluctance to permit off-label promotion, although the requirements imposed on manufacturers might be less burdensome.

“Approval-lite” requirements, however, do not just share the advantages of requiring FDA approval for each marketed indication; they also share its pitfalls. Specifically, this kind of regulation might raise the same First Amendment concerns that have plagued the FDA’s prohibition of off-label promotion. Indeed, shortly after *Amarin*<sup>96</sup> was decided, Pacira Pharmaceuticals sued the FDA in the Southern District of New York, arguing not only that the FDA’s prohibition of *its* off-label speech violated the First Amendment, but also that the analysis in *Caronia* applied equally to the FDA’s requirement that *comparative* claims be supported by substantial evidence.<sup>97</sup> Pacira’s argument seems to be correct: The arguments made in *Caronia* are entirely applicable. The requirement restricts speech, and the obstruction of the flow of information to physicians may actually harm patients’ health, and so the restriction would not be narrowly tailored.<sup>98</sup> The court did not get an opportunity to decide the matter, however, because the FDA settled with Pacira.<sup>99</sup>

Some might argue that if the manufacturer does not conduct testing of off-label uses sufficient even for a reduced form of approval, then any representations that manufacturers make about those uses should be considered false and misleading and therefore unprotected

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<sup>94</sup> See Benlylin Final Order, 44 Fed. Reg. 51, 518 (Aug. 31, 1979) (“These requirements [of at least two studies] are founded upon a basic proposition of science that an experiment must be reproducible in order for the results to be considered valid.”).

<sup>95</sup> See *infra* notes 152–53 and accompanying text.

<sup>96</sup> *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 196 (S.D.N.Y. 2015) (applying the holding of *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012)).

<sup>97</sup> See Compl. ¶ 205, *Pacira Pharm., Inc. v. FDA*, No. 1:15-cv-07055, 2015 WL 5256628 (S.D.N.Y. 2015).

<sup>98</sup> For a more complete treatment of the argument, see *Caronia*, 703 F.3d at 166–69.

<sup>99</sup> *Pacira Pharmaceuticals, Inc.*, News Release, *Pacira Pharmaceuticals Announces Favorable Resolution with U.S. Food and Drug Administration, Which Reaffirms the Broad Indication for EXPAREL* (Dec. 15, 2015), [http://investor.pacira.com/phoenix.zhtml?c=220759&p=irol-newsArticle\\_print&ID=2122491](http://investor.pacira.com/phoenix.zhtml?c=220759&p=irol-newsArticle_print&ID=2122491).

by the First Amendment.<sup>100</sup> Under this argument, any statement made without supporting clinical data is based on speculation and is therefore necessarily misleading.<sup>101</sup> In *Caronia*, however, the Second Circuit appeared hostile to such an argument, stating that off-label promotion “is not in and of itself false or misleading.”<sup>102</sup> Future courts considering the validity of “approval-lite” regulations could conceivably distinguish *Caronia* on two grounds. First, the *Caronia* court expressly noted that, in that case, the government did not argue that off-label speech is always false or misleading.<sup>103</sup> Second, one might argue that an extremely rigorous, full preapproval testing process is not necessary to render a claim not false or misleading, but that *some* evidence for the claim is required. Perhaps claims unsupported by even the comparatively minimal testing requirements of the “approval-lite” regime would be so unsupported by evidence as to be false and misleading, at least in the time period before real-world patient data is sufficiently robust to prove or disprove the claims. This distinction, however, likely misunderstands the reasons that the Second Circuit dismissed this argument in *Caronia*. The Second Circuit appeared to be concerned not with the extreme burden of full clinical testing, but rather with the idea that *any* clinical testing is required to establish that a claim is true and non-misleading.<sup>104</sup> At most, real-world patient data would suffice. Especially in light of the expanding scope of the First Amendment, this argument would likely fail to save “approval-lite” regulations from the same fate as the regulations challenged in *Caronia*.

### III

#### COMMON-LAW INCENTIVES TO TEST

The administrative state is not the only part of government capable of regulating the pharmaceutical industry. The courts, too, can set rules, within the framework of tort law, for the manufacture and distribution of pharmaceutical products, and when manufacturers fail to abide by those rules, courts can impose liability both to compensate

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<sup>100</sup> See Greene, *supra* note 55, at 690–700 (arguing that off-label promotion does not merit First Amendment protection because it is inherently misleading).

<sup>101</sup> See generally Waxman, *supra* note 55, at 306–10 (arguing that there is adequate evidence to sustain the constitutionality of promotional restrictions on off-label marketing).

<sup>102</sup> *Caronia*, 703 F.3d at 165.

<sup>103</sup> See *id.* at 165 n.10 (“The government does not contend that off-label promotion is in and of itself false and misleading.”).

<sup>104</sup> The Second Circuit did not suggest that *some* degree of testing is required to render an off-label claim neither false nor misleading. Instead, it flatly asserted that “the promotion of off-label drug use is not in and of itself false or misleading.” *Id.* at 165.

manufacturers' victims and to deter others from adopting negligent or reckless practices. In this Part, I argue that courts should find that pharmaceutical manufacturers have a common-law duty to test their drugs for each use for which they choose to market them. At the very least, a duty to test would give harmed parties hope of recompense for their injuries. Moreover, by imposing a cost on manufacturers who fail to adequately test their drugs, the common law would provide an incentive to conduct testing at the outset. Even if the testing conducted would not meet the FDA's requirements, it would likely reveal the drug's most apparent risks to physicians. If nothing else, the increased production of data about the drug would better enable the FDA to sanction false and misleading speech.

In Section III.A, I will briefly explain the nature of this duty and why it is superior to the regulatory options discussed in Part II. In Section III.B, I will demonstrate why a common-law duty to test is a defensible extension of existing products liability doctrine. Finally, in Section III.C, I will respond to counterarguments about the workability and enforceability of the duty to test.

#### A. *Proposed Duty to Test*

In my view, courts should hold that under tort law, pharmaceutical manufacturers owe their consumers a duty to test their drugs for each use for which they market them. If manufacturers fail to adequately test their drugs for each marketed use, then courts may hold them liable for the damages caused by their breach of duty. If reasonable testing would have revealed side effects from which patients suffered, and if the patients would not have taken the treatment had they known of the side effect, then manufacturers would be held liable for the patients' damages—and, depending on the facts of the case, may even face punitive damages. This duty would most easily be construed as an element of manufacturers' duty to warn consumers of their products' dangers, as courts have primarily discussed existing duties to test in the context of the duty to warn.<sup>105</sup> However, if the duty were so limited, it would account for damages caused by a lack of safety, but not by ineffectiveness.<sup>106</sup> In order to encompass damages caused by ineffectiveness, courts might hold that when testing would have revealed a drug's ineffectiveness, that drug suffers from a defective design.

Such a common-law duty does not suffer from the disadvantages of the regulatory solutions discussed in Part II. First, such a duty to

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<sup>105</sup> See *infra* Section III.B.

<sup>106</sup> See *supra* note 32 and accompanying text.

test could effectively maintain manufacturers' incentives to test—indeed, products liability duties are designed to create incentives. Avoiding significant monetary liability is a stronger incentive for profit-driven pharmaceutical manufacturers than a labeling requirement would be.<sup>107</sup> Moreover, litigation provides a public forum to expose a manufacturer's inadequate clinical tests, which could provide a public-relations incentive to adopt responsible testing practices.

Second, a common-law duty to test would avoid the First Amendment concerns raised by the regulations challenged in *Caronia*. A common-law duty to test is less suspicious under the First Amendment than are regulatory prohibitions for two primary reasons. First, the regulation challenged in *Caronia* was criminal, not civil—Alfred Caronia was challenging his criminal conviction for mislabeling—and courts give special scrutiny to laws that impose criminal penalties for speech. Second, courts have typically found the First Amendment inapplicable to products-liability standards requiring manufacturers to warn of their products' risks.<sup>108</sup> Rightly or wrongly, tort liability is treated differently than regulatory prohibitions.

### B. Congruence with Existing Doctrine

Common-law courts can adopt a duty to test pharmaceuticals for marketed uses without creating it out of thin air. It has long been recognized that manufacturers have a duty to warn consumers of the dangers that their products present. Because pharmaceuticals are “unavoidably unsafe products,”<sup>109</sup> whether manufacturers can be held liable for harms they cause turns not on whether the drugs themselves are dangerous, but rather on whether the directions and warnings accompanying the drugs are adequate.<sup>110</sup> Federal law does require

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<sup>107</sup> This incentive, of course, is conditioned upon whether harmed plaintiffs could feasibly enforce their claims against manufacturers, no small task. This criticism is addressed in Section III.B, *infra*.

<sup>108</sup> See, e.g., Ashutosh Bhagwat, *When Speech Is Not “Speech,”* 78 OHIO L.J. 839, 866 (2017) (noting that failure-to-warn liability for prescription drugs “involve[s] imposing liability for the content of speech (or failure to speak), and so seemingly implicate[s] the First Amendment,” but that “no one seems to take seriously even the possibility of a First Amendment defense in such cases”); Leslie Kendrick, *First Amendment Expansionism*, 56 WM. & MARY L. REV. 1199, 1215 (2015) (describing “tort liability for failure to warn about dangerous products” as “an area of law so far seemingly immune to First Amendment expansionism”); see also *United States v. Caronia*, 703 F.3d 149, 168 n.11 (2012) (“Physicians and pharmaceutical manufacturers can be held accountable for off-label drug use through medical malpractice and negligence theories of liability.”).

<sup>109</sup> RESTATEMENT (SECOND) OF TORTS § 402A cmt. k (AM. LAW INST. 1965).

<sup>110</sup> See *id.* (“[An unavoidably unsafe product], properly prepared, and accompanied by proper directions and warning, is not defective, nor is it *unreasonably* dangerous.”).

adequate instructions for use,<sup>111</sup> but the Supreme Court has made clear that state common law is not preempted: Manufacturers may be liable in tort for defective warnings.<sup>112</sup> Both the Second and Third Restatement of Torts recognize the duty to warn,<sup>113</sup> and both state that manufacturers must warn not only of risks of which they are aware, but also risks of which they *should* be aware.<sup>114</sup> The question is how much courts are willing to say that manufacturers should know about their products.

At the very least, manufacturers are expected to be “experts in [their] field.”<sup>115</sup> That is, they have a “duty . . . to keep abreast” of the state of knowledge about their drugs within the scientific and medical communities.<sup>116</sup> Some courts have suggested that this defines the entire scope of manufacturers’ constructive knowledge.<sup>117</sup>

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<sup>111</sup> See *supra* notes 33–36 and accompanying text.

<sup>112</sup> See *Wyeth v. Levine*, 555 U.S. 555, 571 (2009) (holding that failure-to-warn claims are not preempted unless it is clear that the FDA would have rejected an adequate warning). Although, under *Wyeth*, failure-to-warn claims are preempted if there is clear evidence that the FDA would have rejected the proffered warning, if the Court were to adopt the *Caronia* analysis, failure-to-warn claims are arguably *never* preempted. One commentator has argued that, if the First Amendment protects manufacturers’ right to truthfully promote their drugs, it must also protect manufacturers’ right to truthfully warn about their drugs’ risks, regardless of whether the FDA has approved such warnings. See Louis M. Bograd, *Be Careful What You Wish for: Drugmakers, the First Amendment, and Preemption*, TRIAL, Nov. 2015, at 24, 25. If manufacturers have a First Amendment right to provide warnings that the FDA does not require or even permit on labeling, they can be required by common law to provide such warnings. See *id.* at 26 (making the same argument but with respect to manufacturers of generic drugs).

<sup>113</sup> RESTATEMENT (SECOND) OF TORTS § 402A cmt. j (AM. LAW INST. 1965); RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 2(c) (AM. LAW INST. 1998).

<sup>114</sup> See RESTATEMENT (SECOND) OF TORTS § 402A cmt. j (AM. LAW INST. 1965) (“[T]he seller is required to give warning against [risks] if he has knowledge of it, or if by the application of reasonable, developed human skill and foresight should have knowledge, of the presence of the ingredient and the danger.”); RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 2 cmt. m (AM. LAW INST. 1998) (“A seller is charged with knowledge of what reasonable testing would reveal.”).

<sup>115</sup> See *Reyes v. Wyeth Labs.*, 498 F.2d 1264, at 1277 (5th Cir. 1974) (“A drug manufacturer is held to the skill of an expert in his field, and is presumed to possess an expert’s knowledge of the arts, materials, and processes of the pharmaceutical business.”); *McEwen v. Ortho Pharm. Corp.*, 270 Or. 375, 386 (1974) (“[T]he drug manufacturer is treated as an expert in its particular field, and is under a ‘continuous duty . . . to keep abreast of scientific developments touching upon the manufacturer’s product and to notify the medical profession of any additional side effects discovered from its use.” (quoting *Schenebeck v. Sterling Drug, Inc.*, 423 F.2d 919, 922 (8th Cir. 1970)).

<sup>116</sup> *Schenebeck*, 423 F.2d at 922.

<sup>117</sup> Indeed, Restatement (Second) can be interpreted that way. Comment j to section 402A requires that sellers warn of risks of which they know and risks that would be apparent “by the application of reasonable, developed human skill and foresight.” RESTATEMENT (SECOND) OF TORTS § 402A cmt. j (AM. LAW INST. 1965). Although the phrase is unclear, it is reasonable to understand it as not requiring additional testing, especially the kind of rigorous trials required adequately test a drug’s safety.

In *McEwen v. Ortho*, for instance, the Supreme Court of Oregon stated that drug manufacturers' duty to warn is "commensurate" with knowledge expressed in scientific literature or "other available means of communication" in addition to its actual knowledge.<sup>118</sup> In *Basko v. Sterling Drug, Inc.*, the Second Circuit stated that "there is no duty to warn of unknown or unforeseeable risks. . . . [T]he duty to warn depends on when the risk became apparent."<sup>119</sup> The Indiana Court of Appeals adopted *Basko's* reasoning that "a manufacturer cannot be required to warn of a risk unknown to science."<sup>120</sup> The Supreme Court of Connecticut stated that "a manufacturer's duty to warn of dangers associated with its products [generally] pertains only to known dangers."<sup>121</sup> The Supreme Court of Illinois stated that manufacturers must only warn of risks of which they knew or should have known based on the "present state of human knowledge."<sup>122</sup>

Despite the support for such a view, such a position appears to me as logically unsound. Taken to its logical extreme, it is inconceivable that manufacturers' constructive knowledge includes only existing knowledge. If that were true, in the absence of statutes like the FDCA, pharmaceutical manufacturers would owe absolutely no duty to test their drugs and to acquire information about their effectiveness and side effects. Such a result seems patently implausible.

Other sources suggest that manufacturers should have some duty to test their products and expand the state of knowledge. Restatement (Third) of Torts: Products Liability, for instance, states that manufacturers "bear[] responsibility to perform reasonable testing prior to marketing a product" and that manufacturers are "charged with knowledge of what reasonable testing would reveal."<sup>123</sup> The District of Minnesota recognized that "a manufacturer has a duty to inspect and test its products" in order to "discover defects or dangers associated with use of the products."<sup>124</sup> The New York Court of Appeals has stated that "drug manufacturers [do not] enjoy immunity from liability stemming from their failure to conduct adequate research and testing

<sup>118</sup> *McEwen*, 270 Or. at 386.

<sup>119</sup> 416 F.2d 417, 426 (2d Cir. 1969).

<sup>120</sup> *Ortho Pharm. Corp. v. Chapman*, 180 Ind. App. 33, 43 (1979).

<sup>121</sup> *Vitanza v. Upjohn Co.*, 257 Conn. 365, 375 (2001).

<sup>122</sup> *Woodill v. Parke-Davis & Co.*, 79 Ill. 2d 26, 35 (1980) (quoting RESTATEMENT (SECOND) OF TORTS § 402A cmt. k) (AM. LAW INST. 1965).

<sup>123</sup> "[A] seller bears responsibility to perform reasonable testing prior to marketing a product . . . [and] is charged with knowledge of what reasonable testing would reveal. If testing is not undertaken, or is performed in an inadequate manner, and this failure results in a defect that causes harm, the seller is subject to liability." RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 2 cmt. m (AM. LAW INST. 1998).

<sup>124</sup> *Kociemba v. G.D. Searle & Co.*, 707 F. Supp. 1517, 1527 (D. Minn. 1989).

prior to the marketing of their products.”<sup>125</sup> Similarly, the Texas Supreme Court denied a tobacco company defendant’s motion for summary judgment on a claim premised on the company’s negligent failure to test its products and warn the public of its dangers.<sup>126</sup>

When courts have recognized and employed a duty to test pharmaceuticals, that duty has been complementary to—not a substitute for—FDA requirements. In other words, “[t]he federal regulatory scheme and the case law must be viewed as intertwined criteria creating the applicable standard of care with respect to testing drug products.”<sup>127</sup> Courts have applied a “duty to test” in two distinct circumstances, neither of which necessarily indicates a duty to conduct clinical testing when not required by FDA regulations.

First, courts have utilized the common-law duty to test to ensure that manufacturers adequately comply with the letter and spirit of FDA testing requirements.<sup>128</sup> For instance, if the FDA has approved a drug based on incomplete or incorrect information, either because of reckless or negligent errors in testing or calculations, or because of deliberate falsification or concealment of information, manufacturers are likely to be found liable in tort for harms caused by resulting failures to warn.<sup>129</sup> In *Roginsky*, for instance, the pharmaceutical manufacturer was held liable because it miscalculated testing data and failed to report abnormalities to the FDA, and as a result, the plaintiff was not warned of dangerous side effects.<sup>130</sup> Although there is no private right of action for violations of FDA testing regulations,<sup>131</sup> such violations can provide the factual basis for a products liability claim.<sup>132</sup> Because the FDA closely oversees the testing process,<sup>133</sup> however,

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<sup>125</sup> Enright by Enright v. Eli Lilly & Co., 77 N.Y.2d 377, 388 (1991).

<sup>126</sup> American Tobacco Co. v. Grinnell, 951 S.W.2d 420, 437 (Tex. 1997).

<sup>127</sup> G. Marc Whitehead & Thomas E. Sanner, *The Duty to Test*, in PRODUCTS LIABILITY: PHARMACEUTICAL DRUG CASES § 5.02 (Donald E. Vinson & Alexander H. Slaughter eds., 1988).

<sup>128</sup> This does not mean that states may determine that an FDA-approved drug cannot be sold within the state. See *Zogenix, Inc. v. Baker*, 2015 WL 1206354, at \*4 (D. Mass. Mar. 17, 2015) (holding that states may not impose de jure or de facto prohibitions of drugs approved by the FDA). Presumably, this is true even if the manufacturer did not comply with FDA testing protocol. The proper way to raise such concerns is with the FDA itself.

<sup>129</sup> See, e.g., *Roginsky v. Richardson-Merrell, Inc.*, 378 F.2d 832 (2d Cir. 1967).

<sup>130</sup> See *id.* at 845.

<sup>131</sup> *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 487 (1996).

<sup>132</sup> Cf. *Wyeth v. Levine*, 555 U.S. 555, 562 (2009) (noting that the trial judge instructed the jury that they could consider the manufacturer’s compliance with FDA approval as evidence of reasonable care, although compliance was not dispositive).

<sup>133</sup> See 1 O’REILLY & VAN TASSEL, *supra* note 14, § 13:1 (4th ed. 2016) (detailing the extensive approval process).

these kinds of products liability cases are rare.<sup>134</sup>

Second, when the state of scientific knowledge indicates a reasonable possibility that a statistically significant connection exists between a drug and a specific side effect, manufacturers might have a duty to further investigate the veracity of the link. Examples help to illustrate this principle. In *Barson v. E.R. Squibb & Sons, Inc.*, the drug at issue was a progestational agent.<sup>135</sup> There was significant scientific literature suggesting that such class of drugs could harm fetal development.<sup>136</sup> Because the manufacturer should have known that its drug might affect fetal development, it had a duty to warn of that risk or at least test for such effects.<sup>137</sup> Similarly, in *Wooderson v. Ortho Pharm. Corp.*, twenty-one women who were taking oral contraceptives had reported side effects of hemolytic-uremic syndrome, a disease characterized by hemolytic anemia, acute kidney failure, and low platelet count.<sup>138</sup> The FDA had sent a letter to physicians advising them of increased risks associated with oral contraceptives containing more than seventy-five micrograms of estrogen and encouraging physicians to prescribe contraceptives with fifty micrograms or less of estrogen.<sup>139</sup> Because the manufacturer failed to test for or warn of these risks, the court imposed punitive damages.<sup>140</sup> In short, the duty to test is generally triggered only when there is some specific risk that is plausible but not yet certain. In other words, courts have imposed on manufacturers a duty to resolve these "known unknowns," or otherwise to warn anyway. This duty to test is familiar in other contexts. For instance, suppliers of blood transfusions are aware of the risk that blood may be contaminated, and they may be liable if they fail to test for, detect, and remove viruses.<sup>141</sup>

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<sup>134</sup> See Whitehead & Sanner, *supra* note 127, § 5.05 (noting that "[r]elatively few cases deal with breach of the duty to adequately clinically test a new drug" and describing only three "cases which provide some specific examples of clinical testing negligence," two of which did not in fact show negligence).

<sup>135</sup> 682 P.2d 832, 835-37 (Utah 1984).

<sup>136</sup> *Id.* at 836 ("[W]hile there were no tests per se on Delalutin [the drug at issue] prior to 1972, there were tests on other progestational drugs that clearly indicated that progestogens were teratogenic." (footnote omitted)).

<sup>137</sup> *Id.*

<sup>138</sup> 681 P.2d 1038, 1062 (Kan. 1984).

<sup>139</sup> See *id.* at 1062-63.

<sup>140</sup> *Id.* at 1064.

<sup>141</sup> See *Zichichi v. Middlesex Memorial Hosp.*, 528 A.2d, 805, 810-11 (Conn. 1987) ("If a plaintiff can show that the defect in the blood could reasonably have been detected or removed, the plaintiff may well be entitled to recover for the supplier's negligent failure to detect or remove the defect."). But see *Hines v. St. Joseph's Hosp.*, 527 P.2d 1075, 1077 (N.M. Ct. App. 1974) (provider not liable because no existing test could have detected the virus).

Courts have not, however, determined whether manufacturers must conduct clinical testing even when not required by the FDA and when no particular potential risk is apparent. This is perhaps not as surprising as it may seem. Products liability law as we know it did not exist before the FDA's premarket approval regime, and, therefore, it has never fallen to the common law to define the standard for reasonable testing. The FDA sets rigorous requirements to obtain a drug's approval for each indication,<sup>142</sup> and therefore any testing manufacturers' conduct with respect to those uses *must* be "reasonable." In other words, a common-law duty to test would rarely if ever require *more* testing than is required to obtain FDA approval.

Standard tort principles, however, would clearly support finding a duty to test even in the absence of knowledge of an identifiable danger. It is difficult to formulate a principle that defends a duty to test for identified potential side effects but not for side effects that have not yet been identified, at least with respect to pharmaceuticals, which manufacturers know almost always pose some danger.<sup>143</sup> Perhaps the costs of identifying side effects are greater than the costs of verifying the existence of identified side effects, but this argument is undermined by the fact that the FDA clearly believes extensive testing to be critical to health and safety; by the fact that the industry custom is to test drugs for all uses for which manufacturers will market them; and by the fact that prior cases have held manufacturers liable under the common law for cutting corners on FDA-required testing.<sup>144</sup> Finding a duty to test for unidentified side effects would not require revising tort doctrine.

It would be difficult, however, to find a duty to test pharmaceuticals for *effectiveness* within the duty to warn. Manufacturers are typically required to warn consumers only of safety risks, not ineffectiveness. In order to require manufacturers also to test the effectiveness of their products, courts should consider whether defective design claims also encompass duties to test.

Because courts typically discuss the duty to test in the context of the duty to warn, this would be a more significant extension of existing

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<sup>142</sup> See *supra* Section I.A.

<sup>143</sup> See, e.g., Restatement (Second) of Torts § 402A cmt. k (AM. LAW INST. 1965) (noting that pharmaceuticals, "in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use").

<sup>144</sup> See *supra* notes 128–34 and accompanying text. To be clear, it is not the fact that FDA requirements are violated that imposes liability under the common law, but rather the facts that constituted violation of federal regulations have also been held to be unreasonable or negligent. See *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 487 (1996) ("[T]here is no explicit private cause of action against manufacturers . . . and no suggestion that the Act created an implied private right of action . . .").

law, but it would not be entirely without support. Under Restatement (Third), which states that foreseeable risks include those that reasonable testing would reveal, products are “defective in design when the foreseeable risks of harm posed by the product could have been reduced or avoided by the adoption of a reasonable alternative design by the seller or other distributor . . . .”<sup>145</sup> That is, reasonable testing is relevant to claims of both defective warning and defective design. Courts have concurred.<sup>146</sup> Still, finding that defective design claims encompass a duty to test would require expanding the scope of the inquiry into the adequacy of provided instructions and warnings.

Manufacturers are liable for inadequate instructions or warnings only when the failure to warn creates a risk of harm: They are not liable for defects that merely render the product ineffective. The peculiarity of the pharmaceutical context would allow courts to pass this hurdle. Pharmaceuticals are designed to reduce harm, and therefore an ineffective medication necessarily results in a greater risk of harm. In other words, in the pharmaceutical context, the distinction between effectiveness and safety is illusory.<sup>147</sup> Restatement (Third) partially notices this fact, recognizing in the comments that physicians must make decisions based on information about both the benefits and risks of a particular drug.<sup>148</sup> Still, the Restatement focuses on disclosure of risks, not disclosure of effectiveness. Moreover, the Restatement does not expressly provide that courts should consider the drug’s risks and benefits *as compared to other drugs*, the only way to fully counteract concerns that a drug is ineffective. Were courts to recognize the illusory distinction between risks and effectiveness, however, this hurdle is surmountable, especially because the touchstone of failure-to-warn inquiries is whether, were the physician made aware of the information withheld, she would prescribe the drug. There is ample room in that test to consider comparative risks and benefits.

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<sup>145</sup> RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 2(b) & cmt. m (AM. LAW INST. 1998).

<sup>146</sup> See, e.g., *In re C.R. Bard, Inc., Pelvic Repair Sys. Prods. Liab. Litig.*, No. 2:11-cv-00195, 2013 WL 3821280, at \*4 (S.D. W. Va. July 23, 2013) (collecting cases to support proposition that “under the risk-utility analysis for design defects, the duty to exercise reasonable care includes the duty to test the product”).

<sup>147</sup> See *supra* note 32 and accompanying text (demonstrating illusory distinction between safety and effectiveness).

<sup>148</sup> RESTATEMENT (THIRD) OF TORTS: PRODS. LIAB. § 6 cmt. d (AM. LAW INST. 1998) (“When prescribing health-care providers are adequately informed of the relevant benefits and risks associated with various prescription drugs and medical devices, they can reach appropriate decisions regarding which drug or device is best for specific patients.”).

### C. Necessity, Workability, and Enforceability

Critics might argue that a common-law duty to test is not necessary: The testing conducted to obtain approval should suffice. Without a duty to test, however, patients would be severely underprotected.<sup>149</sup> The general testing done in Phase I includes a sample size insufficient to draw scientifically valid conclusions,<sup>150</sup> and it only reveals information about the drug's safety, not effectiveness.<sup>151</sup> Testing done in Phases II and III might be done on a different patient population and potentially with different dosages, treatment schedules, and methods of administration. That testing, too, says nothing about the drug's effectiveness for other, untested indications.<sup>152</sup> At least one study has suggested that most off-label uses have insufficient scientific support,<sup>153</sup> demonstrating that existing clinical data, in fact, does not suffice.

Other critics might note that if courts find a common-law duty to test pharmaceuticals for marketed uses, then they also must determine the *content* of that duty. It may be quite difficult for courts to determine how much testing is required in order to be considered reasonable. This type of determination requires fine-grained policy analysis outside the traditional expertise of common-law courts. It would be extraordinarily difficult for courts to craft and impose *specific* regulations, nor could they impose the FDA's original requirements. It is hard to imagine, for instance, courts dictating the precise number of participants that must be included in the trials. They need not, however, promulgate such specific rules in order to determine whether testing is adequate. Instead, courts can use established legal principles in order to determine whether tests fall within a reasonable range.

One such principle is that manufacturers' duty to warn is "commensurate with the seriousness of the danger. The greater the danger, the greater the duty."<sup>154</sup> Such a principle should also inform the scope of the duty to test pharmaceuticals. Two variables in particular could

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<sup>149</sup> See *supra* notes 56–63 and accompanying text (discussing how safety and effectiveness data generated through clinical trials may be indication specific).

<sup>150</sup> See *supra* notes 16–18 and accompanying text.

<sup>151</sup> See *supra* notes 16–18 and accompanying text.

<sup>152</sup> See *supra* notes 19–31 and accompanying text.

<sup>153</sup> See *United States v. Caronia*, 703 F.3d 149, 179 n.7 (2d Cir. 2012) (Livingston, J., dissenting) (citing Randall S. Stafford, *Regulating Off-Label Drug Use: Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1427 (2008) ("In an examination of off-label prescribing of 160 common drugs . . . most off-label drug uses (73%) were shown to have little or no scientific support.")).

<sup>154</sup> See *Wooderson v. Ortho Pharm. Corp.*, 681 P.2d 1038, 1062 (Kan. 1984); see also *Halphen v. Johns-Mansville Sales Corp.*, 484 So. 2d 110, 115 (La. 1986) ("A manufacturer also has a duty to test and inspect its product, and the extent of research and experiment must be commensurate with the dangers involved."); RESTATEMENT (SECOND) OF TORTS

help courts and manufacturers to determine just how serious the danger of off-label uses is, which in turn should guide both in setting the standard of reasonable testing.

First, one might consider how significantly the off-label use varies from the approved use. If the patient populations are materially different (e.g., children versus adults, those with a serious heart condition versus those without), or if the dosages, treatment schedules, or method of administration significantly vary, it would also be reasonable to expect more individualized testing of the off-label use. The more the circumstances surrounding the off-label uses differ from approved uses, the greater the likelihood that the side effects will differ, the greater the risk associated with the off-label use.

Second, some drugs are inherently more dangerous than others. To the extent that preapproval clinical trials and real-world patient data reveal substantial side effects, manufacturers should be expected to conduct more testing. Manufacturers who follow this guidance when deciding how to study off-label uses will certainly fail to uncover many serious side effects,<sup>155</sup> but at least they will have discovered and warned of some.

Finally, critics might argue that the duty to test would not be practically enforceable. Although plaintiffs must satisfy a significant burden in all failure-to-warn claims, injured patients might find it particularly difficult to hold a manufacturer liable for failing to adequately test its drugs. First, the plaintiff must prove that the drug actually causes the side effect from which the plaintiff suffers. But, if the manufacturers did not test the drug, there may be insufficient information to prove that the drug causes the side effect. Second, the plaintiff would have to prove that reasonable testing would have revealed the side effect. But even drugs that undergo rigorous testing and obtain FDA approval carry risks that only become apparent when used by patients.<sup>156</sup> Plaintiffs who suffer from side effects that are conspicuous and reveal themselves quickly are far more likely to recover

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§ 298 cmt. b (AM. LAW INST. 1965) (“[T]he care which it is reasonable to require of the actor varies with the danger involved in his act, and is proportionate to it.”).

<sup>155</sup> For instance, an anti-arrhythmic drug when prescribed to treat “minor disturbances in patients who recently had heart attacks” increased patients’ risk of death by two-and-a-half times. See *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 56–57 (D.D.C. 1998). In that case, both patient populations had heart problems, and there was no evidence that the drug had particularly severe side effects.

<sup>156</sup> See FDA, Merck, and Vioxx: *Putting Patient Safety First?: Hearings Before the Senate Comm. on Finance*, 108th Cong. 49 (2004) (statement of Sandra L. Kweder, Acting Director, Office of New Drugs, FDA) (“Experience has shown that the full magnitude of some potential risks do not always emerge during the mandatory clinical trials conducted before approval . . .”).

damages, because such side effects are more likely to be captured by testing. Although in theory the class-action vehicle might help spread the high costs of proving both of these elements, questions of specific causation would preclude certification of class actions in a high fraction of cases.<sup>157</sup> Each of these burdens is in addition to the difficult task of proving specific causation: The plaintiff must prove that, had a warning been provided, she would not have chosen to take the drug, and that the drug actually *did* cause *her* side effect.

These problems are not insurmountable. Plaintiffs do routinely recover in failure-to-warn cases, and some commentators have suggested a burden-shifting framework to make it easier for plaintiffs to recover on meritorious claims. In the toxic tort context, Professor Wendy Wagner has argued that manufacturers who fail to test their products should bear the burden to prove that their products did *not* cause the plaintiff's injury. "The plaintiff thus establishes a prima facie case with proof of the following: (1) inadequate minimal testing on a product, (2) normal or foreseeable exposure to the product, and (3) serious harm that might be causally linked to exposure to the product."<sup>158</sup>

To address this concern, it would be sensible to adopt a similar rule for pharmaceutical products, especially because it is the pharmaceutical manufacturer's own breach of its duty to test its products that impedes plaintiffs' recovery. If a plaintiff proves that a drug's testing was grossly deficient,<sup>159</sup> that the manufacturer promoted the drug to treat the condition for which the plaintiff used it, that the serious side effect is plausibly linked to exposure to the drug, and that the manufacturer did not warn of the risk, shifting the burden to the manufacturer would resolve many of the most difficult enforcement problems. Manufacturers can easily address any concern regarding excessive liability arising from this burden-shifting framework even without conducting tests sufficient to meet the standard of care. The burden remains with the plaintiff unless their testing was obviously and significantly inadequate.

## CONCLUSION

The regulations proscribing manufacturers' off-label speech are loosening. Those who have pushed for this change believe that

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<sup>157</sup> See *Amchem Prods., Inc. v. Windsor*, 521 U.S. 591, 624 (1997) (holding that the predominance and superiority requirements for class certification was not met because each class member's claims raised different questions of specific causation).

<sup>158</sup> Wendy E. Wagner, *Choosing Ignorance in the Manufacture of Toxic Products*, 82 CORNELL L. REV. 773, 834–35 (1997).

<sup>159</sup> It seems excessive to shift the burden for de minimis breaches of the duty to test.

patients will benefit from off-label promotion, as physicians will have better access to real-world patient data. It is undeniable, however, that if manufacturers may promote their drugs for an indication without first obtaining FDA approval for or even conducting clinical tests of the drug for that indication, they will have a lesser incentive to conduct tests. Whatever one thinks of the ultimate wisdom of permitting off-label speech, such a policy carries a risk that there will be reduced clinical testing. If manufacturers test new drugs for fewer indications, then physicians will have less data upon which to base their prescription decisions, at least until sufficient real-world patient data accumulates. In the meantime, physicians would make treatment decisions under conditions of greater uncertainty, and health outcomes may suffer.

In this Note, I am the first to take as given that manufacturers increasingly will be able to promote their drugs for off-label uses. I have focused on the options available to courts and regulators that seek to maintain the incentives to test despite the increasing acceptance of off-label promotion. The best option available, I argue, lies in the common law: Courts can and should impose on manufacturers a duty to test their drugs for every marketed use. The extent of the testing required should depend on the known dangerousness of the drug and the similarities between the approved and unapproved conditions and the populations afflicted by them.

This solution is not without shortcomings. Judges and courts are not experts in pharmaceutical development. They will make mistakes, and they will be unable to promulgate precise instructions on the testing required. Rights contingent on private prosecution are also routinely underenforced. Although the burden-shifting framework discussed in this Note would help, it would not be a complete solution. Tort doctrine will not be able to incentivize testing as effectively as a prohibition on off-label promotion, but it is the best option available, and it would protect patients from the parade of horrors that many critics of the Second Circuit's decision in *Caronia* fear.