Do Off-Label Drug Practices Argue Against FDA Efficacy Requirements?

A Critical Analysis of Physicians’ Argumentation for Initial Efficacy Requirements

By

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*Complete set of survey written responses is available at:*

[http://mason.gmu.edu/~atabarro/](http://mason.gmu.edu/~atabarro/)

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Do Off-Label Drug Practices Argue Against FDA Efficacy Requirements?

Abstract: The amended Food, Drug and Cosmetics Act requires efficacy certification for a drug’s initial uses (“on-label”), but does not require certification before physicians may prescribe the drug for subsequent uses (“off-label”). Does it make sense to require FDA efficacy certification for new drugs but not for new uses of old drugs? Using a sequential online survey we carried on a “virtual conversation” with some 500 physicians. The survey asked whether efficacy requirements should be imposed on off-label uses; almost all physicians said no. It asked whether the efficacy requirements for initial uses should be dropped, and most physicians said no. We then asked respondents whether opposing efficacy requirements in one case but not the other involved an inconsistency. In response, we received hundreds of written commentaries. We organize and discuss these commentaries with an eye to understanding how the medical market certifies off-label drug uses and how this compares to FDA certification. Does off-label medicine suggest that efficacy requirements should be placed on new uses of old drugs? Does it suggest that efficacy requirements on new drugs should be lifted? We explore these questions, and ask whether the response of many of the doctors exhibits the familiar behavior bias toward the status quo.

Keywords: Food and Drug Administration, drug approval, efficacy requirements, off-label uses, on-label uses, certification, liberalization.

JEL code: I18.
Do Off-Label Drug Practices Argue Against FDA Efficacy Requirements?

I. Introduction

The Food, Drug and Cosmetics Act of 1938 with amendments in 1962 forbids new drugs from being sold unless they have passed FDA-approved tests for safety and efficacy in a specified use, called the “on-label” use. Physicians are allowed, however, to prescribe an FDA-approved drug not only for its on-label use, but also for other “off-label” uses. It often happens that physicians and researchers discover new uses for a drug after it has been permitted, so off-label use is quite common.

Amoxicillin, for example, has an on-label use for treating respiratory tract infections and an off-label use for treating stomach ulcers. For the on-label treatment of respiratory tract infections, amoxicillin has been tested and certified in all three phases of the FDA’s Investigational New Drug clinical study; phase I trials for basic safety and phase II and phase III trials for efficacy. For the treatment of stomach ulcers, however, amoxicillin has not gone through FDA phase II and phase III trials and thus is not FDA certified for this use. Amoxicillin will never go through FDA efficacy trials for the treatment of stomach ulcers because the basic formulation is no longer under patent. Yet any textbook or medical guide discussing stomach ulcers will mention amoxicillin as a potential treatment, and today a physician who did not consider prescribing amoxicillin or other antibiotics for the treatment of stomach ulcers would be considered negligent.

Off-label prescribing is very common in all areas of medicine. It is not uncommon for a drug to be prescribed more often off-label than on-label. Thalidomide
has been approved for use in treating leprosy but is much more commonly used to treat multiple myeloma and AIDS. Most cancer and AIDS patients are given drugs that are not FDA certified for the prescribed use (GAO 1991; Brosgart et al. 1996). In a large number of fields, a majority of patients are prescribed at least one drug off-label (Tabarrok 2000: 26).

To explore the policy lessons of off-label usage, we tapped the knowledge and judgment of actual practitioners. We asked physicians, *Should the FDA hold drug uses to efficacy requirements?*, both as the question applies to initial (on-label) uses and as it applies to subsequent (off-label) uses. Virtually all opposed imposing efficacy requirements on subsequent uses. But the majority of respondents supported the FDA efficacy requirements on initial uses.

Is it inconsistent to favor efficacy requirements for new drugs but not for new uses of old drugs? We asked the physicians to justify their responses in an open-ended format, and received hundreds of justifications of their opinions about FDA policy. The key feature of our study is asking physicians the justification question.


Again, when the FDA evaluates a new drug, the evaluation of safety and efficacy is made with respect to a specified use. Once a drug has been permitted, physicians often come to prescribe the drug for other uses.
But there seems to be a logical inconsistency in allowing off-label uses and requiring proof of efficacy for the drug’s initial use. Logical consistency would seem to require that one either

(1) be in favor of allowing physicians to prescribe off-label and of allowing physicians to prescribe (and pharmaceutical companies to make and sell) new drugs that have not been FDA efficacy certified,

or

(2) be against allowing physicians to prescribe off-label and against allowing physicians to prescribe (and pharmaceutical companies to make and sell) new drugs that have not been FDA efficacy certified.

But even if logic dictates as such, it would not tell us whether to favor (1) or to favor (2). Tabarrok (2000) argues that off-label usage provides a “natural experiment.” In a sense, off-label uses are regulated according to the pre-1962 rules, under which the FDA held new drugs only to safety requirements, whereas on-label uses are regulated according to the post-1962 rules. Thus, the same medical institutions – in the same country at the same time – are operating under dual systems of drug regulation. Off-label prescribing gives us an idea of how medical affairs would proceed in a world in which new drugs were allowed until banned, rather than banned until permitted. Since physicians appear to support off-label prescribing, Tabarrok argues in favor of consistent option 1.

Shapiro (1979) also recognizes the inconsistency in current regulation, but draws a lesson opposite from Tabarrok. Shapiro (p.801) calls the freedom to prescribe off-label
“a regulatory anomaly which deprives some drug consumers of the protection of the [Food, Drug and Cosmetic] Act.” He argues for tightening restrictions on off-label prescribing. Such a position has also been taken by the FDA, although since 1982 the FDA has focused its efforts on limiting pharmaceutical manufacturers rather than physicians. The principle of consistency gives rise to dual arguments for reform, as shown in Figure 2.

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2 In 1972, for example, the FDA announced that there were no extant controls on off-label prescribing but that “when an unapproved use of a new drug may endanger patients or create a health hazard” it was “obligated” to act. Thus, it proposed a proceeding to create controls. It planned to consider the following new rules: revoking the approval of any drug extensively used off-label; regulating off-label uses as experimental (just as if the drug was a new drug); and limiting distribution channels to hospitals or physicians with special qualifications. The medical profession, including the AMA, objected vociferously, however, and the FDA backed down. Over the next decade the FDA asked Congress for similar powers but was not successful. On the 1972 episode see Shapiro (1979) and Christopher (1993). David Kessler (1978), prior to becoming FDA commissioner, also supported restrictions on off-label prescribing, and under his leadership in 1991 the FDA indicated that it was re-examining the off-label question but no new rules materialized.

3 In 1982 the FDA issued a bulletin formally stating that it condoned off-label use as "accepted medical practice." 12 FDA Drug Bull. (United States Food and Drug Admin., Washington, D.C.), Apr. 1982, at 4 but this has not precluded significant FDA impact on off-label usage, as FDA tightly restricts manufacturers’ speech about off-label uses.
Our survey drew physicians into this debate. One physician responded by quoting Emerson: “A foolish consistency is the hobgoblin of little minds.” Like more than 150 responding physicians, he gave his reasons for deeming the consistency argument for liberalization flawed or imperfect.

III. The Survey and the Main Quantitative Results
Survey Logistics

We drafted the questionnaire so as to pose the two main policy questions and then the consistency argument. We hired HostedWare.com to host the survey online. The questions were presented sequentially: Each important question appeared on its own Web image and the respondent had to provide his or her answer before viewing the next question. The survey limited responses to one-per-computer. To get physicians to access and complete the survey, we hired Medical Marketing Services to send an e-mail message to 8000 physicians. The broadcast message invited the physician to aid academic research on pharmaceutical regulation by accessing and responding to the brief questionnaire at the URL provided. The message asked the recipient not to share the URL with others. We instructed Medical Marketing Services to randomly select physicians in certain fields including allergy/immunology, cardiology, endocrinology, neurology, oncology, urology, internal medicine, geriatrics, and pediatrics. The e-mail broadcast yielded 504 physicians who answered at least one question and 492 who completed the survey by answering at least one of the main policy questions (a response rate of about six percent).

When a responding physician clicked on the indicated URL, he came to a simple Web image titled “Opinion Survey on Pharmaceutical Regulation,” and a brief welcoming message about responses being anonymous and used only for purposes of academic research. The respondent clicked “Begin Survey” which led directly to seven preliminary questions about the respondent’s practice.

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4 The cost of the HostedWare services was $710 and the cost of the Medical Marketing Services was $3,752.
The Preliminary Questions

The seven preliminary questions are provided here (the numbering 1 through 7 did not appear in the survey). The response-rate percentages or other summary information are indicated, as is the absolute number of respondents [in square brackets]:

1) What state do you practice in?
47 states in total were represented with the five largest being

<table>
<thead>
<tr>
<th>State</th>
<th>Percentage</th>
<th>Number</th>
</tr>
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<tbody>
<tr>
<td>CA</td>
<td>11%</td>
<td>54</td>
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<tr>
<td>NY</td>
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<td>40</td>
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<tr>
<td>TX</td>
<td>7%</td>
<td>34</td>
</tr>
<tr>
<td>FL</td>
<td>5%</td>
<td>26</td>
</tr>
<tr>
<td>NC</td>
<td>4%</td>
<td>22</td>
</tr>
</tbody>
</table>

2) How many years have you been in practice?
The distribution was described by the following:

<table>
<thead>
<tr>
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<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum</td>
<td>0</td>
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<tr>
<td>Maximum</td>
<td>48</td>
</tr>
<tr>
<td>Mean</td>
<td>16</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>11</td>
</tr>
</tbody>
</table>

3) What are your areas of clinical specialization?
After collapsing multiple responses into single responses (e.g. Hematology/oncology is listed under oncology) and subsuming pediatric [blank] into pediatrics (e.g. pediatric oncology and pediatric allergy are both listed under pediatric) the top five categories were:

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal Medicine</td>
<td>29%</td>
<td>142</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>28%</td>
<td>138</td>
</tr>
<tr>
<td>Cardiology</td>
<td>9%</td>
<td>46</td>
</tr>
<tr>
<td>Neurology</td>
<td>9%</td>
<td>44</td>
</tr>
<tr>
<td>Oncology</td>
<td>8%</td>
<td>38</td>
</tr>
</tbody>
</table>

4) Are you employed at or affiliated with a teaching hospital?

- Yes: 58% [288]
- No: 41% [203]

5) Most physicians have careers principally as practitioners and some are also involved in doing and publishing medical research (some also teach, but let’s put that aside). Of the following choices how would you describe your career.

a. Strictly practitioner, not a researcher: 46% [228]
b. Mainly a practitioner, only limited involvement in research: 38% [188]
c. About half practitioner, half researcher: 11% [52]
d. Mainly a researcher (with, of course, some practice along the way): 2% [10]
e. Not sure/ Not applicable: 3% [14]

6) When the FDA approves a drug, it does so for a certain specified use. Often the drug is later found to have other uses, known as off-label uses, for which physicians may also prescribe the drug.
How often do you prescribe drugs for off-label indications?

- a. More than 40 percent of my prescriptions are off-label: 9% [44]
- b. Between 30 and 40 percent: 12% [60]
- c. Between 20 and 30 percent: 17% [83]
- d. Between 10 and 20 percent: 19% [92]
- e. Between 5 and 10 percent: 18% [91]
- f. Less than 5 percent: 18% [88]
- g. Don’t know/ Not sure: 7% [34]

7) In your medical practice, do you treat children?

- a. Never: 33% [161]
- b. Rarely: 20% [100]
- c. Sometimes: 10% [50]
- d. Often: 7% [34]
- e. Always: 29% [147]

Our survey was not intended to be a random sample of all physicians nor was that necessary for our purposes. Instead, we wanted to receive responses from a diverse group of physicians.

**The Two Main Questions**

Next, the respondent encountered the two main questions. One asked about the imposing of efficacy requirements on off-label uses:

What would be your position on a proposal to change FDA law so that physicians could *not* prescribe drugs for off-label uses? Would you favor or oppose such a change?

- Favor: 2% [12]
- Oppose: 94% [460]
- Don’t know/ Not sure: 4% [20]

Of 492 physicians answering the question, 460 opposed ending the freedom to prescribe off-label. Even though the respondent yield from the broadcast email message

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5 Reported rates of off-label prescribing should not be used as estimates of off-label prescribing because physicians often do not know whether an indication is off-label. The Appendix here shows that reported rates correlate with support for FDA liberalization.
was low and the sample not fully random across all physicians, we are nonetheless reasonably comfortable in concluding that nearly all physicians favor being allowed to prescribe off-label. In addition to our survey, physician groups such as the American Medical Association have long opposed restrictions on off-label prescribing. Thus, George Lundberg, then the editor of the *Journal of the American Medical Association*, testified in Congress:

“[p]rescribing FDA-approved drugs for off-label (unlabeled) uses often is necessary for optimal patient care. For a product to have the most effective potential benefits, law and regulation should and must follow, not precede, science. There are too many variations in clinical circumstances and too much time delay in regulations to allow the government to impede the physician’s ability to practice in these regards when it is medically appropriate.”

In addition, several respondents volunteered strongly worded objections to the idea of banning off-label prescribing. Such a reform would be “clearly naïve,” “stupid and unethical,” “dangerous,” “disastrous,” and “medicine would grind to a halt.”

Given the strong support for off-label prescribing we can predict that physicians will not accept Shapiro’s consistency argument for further FDA control. It does not follow, however, that they will accept the economist’s consistency argument for liberalization.

The other main question asked about dropping the efficacy requirements on initial uses:

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6 Analysis of the complete responses suggests that a number of the 32 physicians who answered either “Favor” or “Don’t know/ Not sure,” had actually gotten confused and got “the sign” wrong when answering the question.
8 The remarks come from written comments f63, g58, f157, f47, and f51. (“f63” means the 63th final comment. “g58” means the 58th challenge. Elsewhere we indicate “consistent” comments with a “c.”) Here and elsewhere we take the liberty of correcting spelling and occasionally improving minor punctuation. The respondents’ written comments are available online in their original form.
Under current law, when the FDA reviews an application for a new drug, it holds the drug to both safety and efficacy requirements before permitting the drug.

What would be your position on a proposal to change FDA law so that physicians could prescribe a new drug once the current FDA safety requirements had been met? Under this system, manufacturers and researchers could continue with efficacy certification (from the FDA or some other institution) if they so choose, but physicians would not be prevented from prescribing drugs that did not have efficacy certification from the FDA.

In brief, what would be your position on a proposal to make the FDA efficacy standards an optional form of certification, rather than a requirement as at present?

- Favor 27% [133]
- Oppose 58% [284]
- Don’t know/ Not sure 15% [75]

Given how little the average American questions the FDA, it may be surprising that 42 percent of the respondents were not decidedly in favor of retaining initial efficacy requirements, and 27 percent favored eliminating FDA efficacy requirements. The sample is small and not necessarily representative (albeit not biased with respect to our questions in any obvious way) but the numbers are consistent with previous studies. The Competitive Enterprise Institute in Washington DC has posed a very similar question in six nationally representative telephone surveys of physicians conducted by The Polling Company. After asking several questions which do bring out the costs of drug

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9 (This note was not included in the survey.) Physicians in the U.S. may prescribe drugs that have not been FDA approved (such prescriptions might be filled by pharmacies abroad or domestic institutions engaged in drug trials). In practice, however, a physician’s ability to prescribe a drug is tied to the manufacturer’s right to market and sell the drug in the U.S. To keep our survey questions from becoming overly complicated, we often employed phraseology that would suggest that the FDA directly regulates prescribing. We are confident that this simplification did not bias or blur the investigation, as not a single physician remarked on this technicality or appeared to be confused because of it.
restrictions, CEI consistently finds that a majority of physician respondents “Strongly Favor” or “Somewhat Favor” making unapproved drugs and devices “available to physicians as long as they carry a warning about their unapproved status,” while a minority answer “Somewhat Opposed” or “Strongly Opposed”. Our results and those of CEI indicate that there is not a strong consensus among physicians about the desirability of initial efficacy requirements. Here, about 25 percent of physicians are in line with the consistency argument – they favor being able to prescribe off-label and drugs lacking initial FDA efficacy certification. The majority, however, gave “inconsistent” responses.

**The Consistency Argument**

The majority who gave “inconsistent” responses next encountered the following statement and question:

I noticed that you answered in favor of physicians being allowed to prescribe off-label but against physicians being allowed to prescribe new drugs that had met FDA safety requirements but not FDA efficacy requirements.

Because off-label indications have not been FDA-certified for efficacy, some people argue that off-label prescribing is equivalent to prescribing a new drug that has been FDA safety-certified but not FDA efficacy-certified. According to this argument, to be consistent, one should either be in favor of allowing physicians to prescribe off-label “and” allowing physicians to prescribe new drugs that have not been FDA efficacy-certified, or against both kinds of allowances.

How do the following choices best reflect your thoughts on this argument?

- It’s an interesting argument but I would need more time to think about it before responding to it. 7% [19]

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10 Competitive Enterprise Institute 2007 summarizes all six CEI surveys conducted from 1995 to 2007.
11 We varied the survey so that the posing of the two main questions was ordered one way in one survey and the reverse in the other. We found that the order of the questions did not make a significant difference. Thus the precise wording of the consistency question varied slightly depending on the order of the questions.
• The argument makes me less inclined to support off-label prescribing.  4%  [11]
• The argument makes me more inclined to support allowing physicians to prescribe new drugs that have not been efficacy-certified by the FDA.  8%  [20]
• I think the argument is invalid. Letting doctors prescribe off-label differs from the proposed reform of letting them prescribe new drugs that have not been efficacy-certified by the FDA because: [a text-box for open-ended responses followed]  80%  [205]

This presentation of the consistency argument led 12 percent to reconsider their views – with almost twice as many revising in favor of liberalization as opposed to expanding restrictions – but the majority of respondents were unmoved by the argument. This is unsurprising, as few people quickly change their minds upon encountering an argument (especially in an impersonal Web survey).

An assessment of the consistency argument was also solicited from the physicians who gave “consistent” responses:\(^{12}\):

I noticed that you answered in favor of physicians being allowed to prescribe off-label and in favor of allowing physicians to prescribe new drugs that met FDA safety requirements but not FDA efficacy requirements.

Preliminary results from the survey indicate that many other physicians are in favor of off-label prescribing but are against loosening FDA requirements. Since your response differs we would like to explore this in a little more detail.

In particular, we are interested in your evaluation of the following argument.

Because off-label indications have not been FDA-certified for efficacy, off-label prescribing is very much like prescribing a new drug that has met FDA safety but not efficacy requirements. Therefore, one should either be in favor of doctors being allowed to prescribe off-label *and* being allowed to prescribe new drugs that have met safety but not FDA efficacy requirements, or against both allowances.

How do the following choices best reflect your thoughts on this argument?
• I think the consistency argument makes a lot of sense; it agrees with the reasons behind my responses. [Use other box for further response.]

\(^{12}\)We did not get the idea of asking the “consistent” respondents what they thought of the consistency argument until after the survey was in progress. Thus not every consistent respondent encountered this question. The consistency question always came last in the survey (save the final solicitation of final comments), so adding the question could not have changed the distribution of answers to the preceding questions.
We saw that most “inconsistent” respondents rejected the consistency argument. Here we see that most “consistent” respondents accepted it. Indeed, 95 percent saw merit in the argument. However, one ought not count this as a clear endorsement of the consistency argument, because it is likely that a respondent is disposed to sign on to a justification of responses he just made.

Finally, all respondents came to a page inviting them to share any “thoughts or ideas about the questions in the survey,” again in an open-ended format. This provided yet another stream of feedback.

In the Appendix we discuss two correlations – support for FDA liberalization increases markedly among practitioners as opposed to researchers, and support for liberalization increases with reported rates of off-label prescribing. Now we turn to the written comments on the consistency argument.

IV. The “Virtual Conversations”

Of the 205 “inconsistent” physicians who explicitly deemed the consistency argument invalid, 176 wrote something in the “because” box. We read, organized, and posted the complete set of comments online, along with final comments and other remarks from
We have organized the comments into a series of three challenges to the consistency argument. We set out the idea as the respondents themselves would approve; that is, to our best capability we represent their idea fully and faithfully. We then discuss the arguments drawing on the literature on FDA reform as well as material from other physician respondents.

A. The relatedness challenge:

*The pharmacological mechanisms of off-label uses are closely related to those of the on-label uses.*

The most common challenge to the consistency argument involves the idea of related pharmacological mechanisms. The simplest case is out-of-age prescribing:

Off label use can mean using a drug under FDA age limits – for example, Zyrtec in a 1 year old. (g57)

Many off-label uses in my case are in children younger than the approved ages. The efficacy has been tested and proven for the given use, just not in these age groups. (g166)

Indeed, 80 to 90 percent of pediatric patient regimens involve at least one off-label prescription (Jaffe 1994; Kauffman 1996). In making the relatedness argument, 22 physicians specifically cited age classes or pediatrics. But many others presented the

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13 The complete (and organized) set of challenges, “consistent” comments, and final comments can be accessed online at the working papers section of Tabarrok’s web site, [http://mason.gmu.edu/~atabarro/](http://mason.gmu.edu/~atabarro/). Each comment is marked to indicate any relatedness to the challenges. Also, some comments contained no clear theory that we could discern (such as comments that simply restated positions, justify only one of the positions taken by the respondent, or describe the respondent’s own prescription practices).
argument in more general terms, speaking of related mechanisms, similarities of drugs within a given class, proven activeness of the drug, prescribing “by analogy,” and “extrapolating” from on-label to off-label. One physician illustrated the argument thusly:

Some of the newer antihistamines were initially only indicated for the treatment of seasonal allergic rhinitis, but not for perennial allergic rhinitis. Well, there is no difference in the allergic cascade and mechanism of seasonal and perennial allergic rhinitis and their response to antihistamines. Consequently, most allergists prescribed them for both forms of rhinitis before the FDA published its official approval of indications. (g93)

The force of the consistency argument for liberalization comes from the premise that off-label prescribing is *like* prescribing a new drug that has not been efficacy-certified by the FDA. The relatedness argument challenges this premise by arguing that off-label prescribing is not that different from on-label prescribing. In this view, prescribing a drug that has not been FDA efficacy-certified is like searching in the dark while prescribing off-label is like searching in the dusky light cast by the nearby lamp of the on-label use.

**Discussion**

Is it true that most off-label prescriptions are closely related to the on-label prescription? It’s difficult to say because observers can disagree about whether two treatments are “closely related” (see further below). But there is agreement, however, that many off-label uses are *not* closely related to the on-label use. Thalidomide is used on-label for the treatment of leprosy but as one physician wrote “we found by serendipity that it was effective in myeloma and supported by the peer review literature” (g134). Today some 99 percent of Thalidomide prescriptions are for off-label uses quite distinct
from leprosy (Young and Adams 2003). The role of serendipity in discovering off-label testsifies to the unrelatedness of such uses. Minoxidil, for example, was developed as a drug for the treatment of hypertension but after users reported unusual hair growth it later became much more widely used off-label and then under the brand name Rogaine as a treatment for baldness.

Another physician wrote:

We frequently find uses for drugs that the FDA has not realized yet. A good example is the use of verapamil for treatment of headaches. This was initially (and still is) primarily a cardiovascular drug, however patients started reporting that their headaches had improved or gone away while on this drug, so it was a simple step for physicians to begin trying this drug for a different indication. I don't know that the FDA has ever approved this drug for headaches [it has not - the authors], but we use it, and it works. (g14)

The unrelatedness of much off-label prescribing is acknowledged by both those who defend and those who oppose or defend off-label. Consider, for example, the following defense written by Tabarrok14:

Decades ago, quinacrine was approved for malaria, and chlorpromazine for schizophrenia. Both drugs have recently been found to be potential treatments for Bovine-Creutzfeld-Jakob disease (BJD), commonly known as mad-cow disease. Because these drugs were already approved for another use, BJD patients could begin taking them within months of the publication of scientific papers suggesting their effectiveness. If these drugs had been new they could not have been marketed until completion of FDA approved clinical trials – a process that could have taken a decade or more. Indeed, BJD is rare, so the cost of this process would almost certainly have kept any company from funding the necessary trials. The drugs could be prescribed as soon as physicians and patients evaluated the risk-return tradeoff favorably only because they had been permitted for other uses. With respect to treating BJD, quinacrine and chlorpromazine were essentially new drugs. Why should other patients, not so lucky as to be in need of an old drug with new uses, not have access to new drugs on the same terms?

Now consider the following story from a Knight-Ridder investigative report (Young and Adams, 2003):

For the last three and a half months she was pregnant, Tammie Snyder had a small medical device strapped to her thigh. It pumped a drug called terbutaline through her body to prevent her from going into labor too soon. On Sept 17, 2002, Snyder gave birth to two healthy girls. Within days, however, her lungs filled with fluid, her heart began to fail and she was told she might need a heart transplant. She recovered, but she’s been told she can never have a baby again. Her heart wouldn’t stand the strain. Terbutaline is an asthma drug, and the Food and Drug Administration hasn’t approved its use to prevent premature labor. The FDA has warned doctors that the treatment is “potentially dangerous” and may not be effective. Snyder said her doctor never told her about the warning or that the FDA had approved terbutaline only to treat asthma.

The first story focuses on the benefits of off-label prescribing and the second on the costs but both stories acknowledge that off-label prescribing can depart considerably from FDA approved-uses. Similarly, one physician wrote: “Most of the drugs I use for diseases such as lupus, AS, Reiters, Behcet’s, vasculitis, etc etc etc are off-label” (g104). Surely, this doctor’s therapeutic arsenal is not based chiefly on sure thing extrapolation from on-label indications. Throughout the responses, physicians provided many examples – antileukotrianes, verapamil, Amiodarone, elavil, plaguenil, cyclobenzaprene, Depakote ER (g107, g14, g20, g58, f157, c11) – in which important off-label uses – though perhaps related to – were not direct or certain extrapolations from the on-label uses.

The relatedness challenge fails as a positive statement of how off-label prescribing works – in any reasonable metric, much off-label prescribing is unrelated to on-label prescribing.15 Although the relatedness challenge fails as a positive statement of

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15 Furthermore, “relatedness” is a tricky concept and its presence (or absence) may be more obvious ex-post than ex-ante. Prozac, for example, is used on-label to treat depression but it is also prescribed off-label for the treatment of alcoholism. Are these treatments related? Since the etiology of neither depression nor alcoholism is well understood one could not conclude on the basis of theory that these diseases were related. Indeed, one of the few reasons to think that these diseases bear some relation to one another is that Prozac has had some limited success in treating both (Naranjo et al. 1988). In this case, relatedness, to the extent that it exists, is more suggested by off-label prescribing than a cause of such prescribing. It’s also
how off-label prescribing works perhaps it can be understood as a statement about how off-label prescribing should work. Physicians who invoke the relatedness argument might agree that if an efficient way were found for an official body to deem off-label uses either “related” or “not related” to the on-label uses, then it would be desirable to have new policy rules that freely allowed related uses but imposed new efficacy requirements on “not related” uses. That is the implication of the relatedness argument, but, once put this way, would the physicians really embrace it? Later, we examine in more detail whether the consistency argument might better be resolved by favoring more FDA control, contra the physicians stated preferences.

B. The Cognitive Saturation challenge

Dropping efficacy requirements would flood the market with ineffective drugs; pharmaceutical companies would promote ineffective drugs and push them on patients and doctors, saturating their cognitive abilities to sort out good indications from bad.

These physicians are concerned that dropping the initial requirements would bring a “flooding” of the market with ineffective drugs.\(^\text{16}\) “[T]hat’s what the makers of Aspercreme and Icy Hot are for!”\(^\text{16}\) (g87). Several made reference to the “chaos” of dietary supplement or herbal remedies (e.g., g29, g69, g73). The job of medical science

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\(^{16}\) The term “flood” is used by g55, g87, g90, g148; and the concern is similarly expressed by many other challenges (see especially those in the PromoHaz section of the listing online).
and practice is to sort out good from bad, but the cognitive resources of the medical nexus are limited, of course. The greater the number of new drugs, and the greater the proportion of ineffective drugs, the thinner will these cognitive resources be spread. A rapid influx of new products could lead to treatment practices that are based on a shallower base of clinical experience, which would increase the error rate and impair the collective learning process.

Discussion

The physician arguments are logical explanations for why they oppose the dropping of efficacy-requirements but they do not address the heart of the consistency argument. Fear of a flooding of the market and consequent cognitive saturation appears to be inconsistent with the very extensive support that all physicians gave for off-label prescribing. Today, all the drugs that have been permitted are available on the market and collectively constitute an ocean of potential off-label treatments for every possible ailment. Yet doctors do not randomly dip into this expanse and prescribe drugs without evidence of effectiveness. Thus, the possibility of many ineffective drugs being available does not really work as a challenge to the consistency argument, because the consistency argument carries the implication: So, then, why not prohibit off-label uses?

Some respondents, however, spoke of a flood of new drugs that would be heavily promoted.

It is now commonplace for drug companies to directly market to the public which could bring unwanted patient pressure to bear on the MD to prescribe for the use not tested for efficacy. (g100)
Many physicians prescribe drugs based on the "flashiest ads" and detail representatives. (g109)

[Physicians sometimes give in to patient requests for medications even though they may not think that the drug is effective. (g119)

[Physicians and consumers alike often enjoy trying the newest, "best" thing on the market; this could allow a significant amount of prescribing of presumably safe pharmaceuticals with questionable benefit. (g148)

Just being safe is deceptive to consumers (patients) and allows pharmaceutical representatives, from whom most physicians seem to get most of their information, to twist information in all kinds of ways. (g124)

Given that 40% of physicians are willing to prescribe whatever the patient asks for, the result would be a mess. (f64)

If medicines were approved without proof of efficacy, this could lead to worsening of the current problems brought on by overaggressive advertising without evidence. (g59)

Physicians would be . . . subjected to barrages of claims from drug companies and would have a lot of difficulty evaluating them for accuracy. Drug companies are notorious for misrepresenting their products. (g14)

[The efficacy requirements prevent] the chaos that now exists with alternative medicine "Natural Herbal Medications" which make unsubstantiated claims as to their potential benefit to the consumer. (g69)

The reform proposal to make efficacy requirements optional, as put in the survey question, did not specify one way or the other how issues of drug promotion would be handled. The respondents presumed that, under the reform, drug companies would enjoy the same promotion privileges that a company today enjoys in promoting the on-label uses of an FDA permitted drug. But it would actually be more in keeping with the consistency argument to suggest that drug companies that did not get FDA efficacy certification for an indication would only be allowed the same (limited) promotional
freedoms that they enjoy today for off-label uses. With this provision, the flooding or
cognitive saturation challenge does not answer the consistency argument.

With similar restrictions on promotion, off-label prescribing and allowing sale of
new drugs with FDA approved safety but not efficacy trials appear to be similar. Even
with this proviso, however, it seems unlikely that the physicians quoted above would
favor dropping efficacy requirements.17 If so, what these physician comments do suggest
is that they think the inconsistency of the status quo ought to be resolved in favor of
greater regulation of off-label prescribing. We take up the issue of how to resolve the
consistency argument at greater length below.

C. The Incentive Challenge:

_Efficacy requirements generate knowledge but because of differential incentives
arising from the temporal limit on patent protection, efficacy requirements suppress
fewer drugs when placed on initial uses than they would if placed on subsequent
uses. This difference recommends opposite policies in the two cases._

Many doctors responded to the consistency argument by saying, absent initial
efficacy requirements, “companies would not have incentives to provide efficacy studies”
(g90). (Physicians also pointed out that FDA efficacy studies also increased knowledge
of safety thus removing efficacy requirements would also diminish safety knowledge.)

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17 We do not take up this discussion here but a substantial body of work by economists and others develops
a respectable case for the self-correcting dynamics and social benefits of the freedom of speech in health
products and foods. See, for example, Leffler 1981; Ippolito and Mathios 1991, 1995; Ippolito and
is not obvious, therefore, that the net effect of promotion of off-label therapies would be negative.
But “there are many instances where the market for a new indication for an old, off-patent drug is too small for a drug company to have any incentive to fund an FDA approval process. Would manufacturers of generic drugs have any economic reason to fund such an approval? In many cases, the answer would be no” (g95).\textsuperscript{18}

FDA efficacy requirements have two effects. The good effect, the “knowledge effect,” is that requirements induce the pharmaceutical company to fund the requisite studies and thereby enhance knowledge beyond the level otherwise attained. Better knowledge may mean more information about specific drugs but also includes the eradication or avoidance of spurious and useless ideas; it alleviates cognitive saturation. The bad effect comes from the increases in costs, delays, and uncertainties in developing and getting the FDA’s permission.\textsuperscript{19} The costs of gaining FDA approval will in some cases discourage industry, science, and medicine from bringing forth the drug or indication. This is the “suppression effect.” Efficacy requirements increase the knowledge about the indications that do become available, but suppresses their number.

The balance of the knowledge effect and the suppression effect, these physicians say, favors initial efficacy requirements because the suppression effect is not so large, since the company will begin selling the drug while the patent is young, and the knowledge effect is large, since apart from clinical testing of the new drug there would be little experience with it. But for subsequent uses the balance opposes efficacy requirements because the suppression effect would large, since the patent is old, and the knowledge effect is not so large, since medicine is learning from the drug’s initial indications.

\textsuperscript{18} Other challenges along these lines are g7, g20, g40, g58, g59, g79, g85, g104, g115, g121, and g134.
\textsuperscript{19} DiMasi, Hansen, and Grabowski (2002) estimate that the average cost of getting a drug to legal status is $800 million. On the uncertainty of obtaining permitting, see DiMasi 2002.
Discussion

A pharmaceutical manufacturer’s willingness to pay for putting a drug through the FDA process depends on the market exclusivity afforded by a patent. If a drug is not under patent, then other firms that did not incur costs of drug development would compete and drive prices below the profit point. Since subsequent uses are discovered after a drug has been on the market for some time, they are discovered when the patent is winding down or has expired. The incentives to fund efficacy studies for subsequent uses dwindle as time wears on – even if the subsequent uses are highly valuable to society as a whole.\(^{20}\) Thus the fact that the patent is winding down is a good argument in favor of not requiring FDA efficacy-certification for off-label prescriptions. In this respect, the incentive challenge supports the status quo but it does not \textit{per se} argue against the dropping of efficacy requirements.

Insofar as the incentive challenge may be construed as a rebuttal to further liberalization, it should be taken to be challenging the argument that markets will supply assurance. The incentive challenge says patents are a necessary \textit{but not sufficient} inducement for producing efficacy studies — to create sufficiency we need FDA efficacy requirements. Here we may quote one of the physicians who favored liberalization responding to this argument as follows: “A pharmaceutical company must support the efficacy of its drugs with clinical research to sell its product” (c22). The pharmaceutical company could not hope for the medical community to adopt its drug into standard care.

\(^{20}\) The FDA can and does grant what are in effect extensions to patents for producing new and valuable research but such privileges are difficult if not impossible to enforce when patents have expired (see Tabarrok 2001 for a discussion of exclusivity privileges).
(or, at least not for very long) without some demonstration of its relative efficacy. It
could not hope to really establish the drug’s indication without serious evidence
recognized by the relevant professional and scientific communities. The dollar value of
the patent on a superior new drug depends not merely on legal permission to supply the
drug and some measure of exclusivity in doing so, but on demonstrating to the medical
community that it is superior.

Moreover, physicians pointed out that medical research is performed and paid for
by many parties other than pharmaceutical companies – universities, large medical
organizations such as HMOs, joint ventures among hospital groups, research non-profits,
government organizations such as the NIH, and others. Physicians may underestimate
the sagacity of their own profession. Economist J. Howard Beales (1996) found that off-
label uses that later came to be recognized by the FDA appeared in the US
Pharmacopoeia on average 2.5 years before FDA recognition. That the US
Pharmacopoeia recognizes off-label indications years ahead of the FDA demonstrates
that physicians and scientists have certified thousands of drug indications quite
independently of the FDA even when those indications are not very closely related to the
original indications. Here are some physicians’ remarks on the wider forms of
recognition and certification used in medicine:

Often efficacy information is already available from studies done outside the
USA. (g47)

There is often data from Europe or in peer review journals. FDA efficacy trials
are important, but they are not the only measure (except legally in terms of
company marketing) of a product’s efficacy for a certain condition. (g28)

Off label use is very often based on valid smaller studies concerning other than
the index medical condition; those studies may not be large enough or the
pharmaceutical company may not want to spend the $ it takes to get FDA approval. (g44)

FDA approval on efficacy lags behind peer-reviewed data that may suggest efficacy. I favor off-label use only if there is reasonable data, or reasonable inference, of efficacy . . . (g50)

Almost all cancer chemotherapy is off-label. There is no way 2 or 3 drug companies can expend the effort to get a combination regimen approved. Oncologists use the peer reviewed literature to decide therapy. Almost always decisions are based on randomized clinical trials. (g53)

Plaquenil was developed and FDA-approved as a malarial drug. Later it was found to relieve Rheumatoid arthritis symptoms in the patients taking it for malaria. Studies show that it worked and was efficacious but should we wait for the FDA to prolong the relief of pain and suffering for several years while the necessary drug company/FDA studies are done or just use common sense? Often there is no financial incentive for a drug company to pursue off label indications for conditions that wouldn’t generate sufficient income to offset the cost of FDA approved trials. But university based, double blind, highly powered studies show benefits that outweigh risks. (g58)

Most of the drugs that I deal with are only approved for one form of cancer. They are then put through trials in other diseases and these are recorded in the literature. Those that show efficacy are then NON-FDA approved but COMPENDIUM approved and are paid for by insurance. (g64)

The off-label experience testifies to the fact that much knowledge about efficacy (and about safety) is produced outside the FDA regulatory apparatus. The natural incentives arising from economic interests, the patient’s self-interest, liability risks, professional pride and esteem, scientific curiosity and competition, and basic human morality create significant incentives to invest in knowledge creation. Initial efficacy requirements, therefore, may induce less net knowledge about new drugs than one would at first suspect. To some degree, initial efficacy requirements merely require what would be done in any case. What matters in the final analysis however is how the knowledge effect compares to the suppression effect.
The Dissidents Speak

A significant minority of physicians staked out a consistent position. Recall first, that 32 percent of respondents with a definite opinion favored the elimination of initial efficacy requirements. And, again, 76 percent of such liberalizers said the consistency argument “makes a lot of sense” plus another 20 percent said “there’s merit” to the argument.

These dissidents from the status quo made many pro-liberalization comments. Here is a sample:

The patients need my help and trust my judgment. If through my own evaluation I find a use for a drug my patients needs, I don't care what opinion of [it] the FDA has. (c6)

I practiced for several years in CentroAmerica where the use of drugs is without any "FDA" approval and never had any problems with the new medication, as a matter fact I remember when we first use Zythromax. (f79)

You might have asked – Are there instances where you can document patient harm by the current process? STI571 for CML is a recent fine example where efficacy and safety data appeared to be present for 6-9 months before actual approval . . . (f140)

There is a direct relationship between the physician and the patient and this allows a more accurate choice of alternative medications to be used in the medical treatment. The FDA is too distant to the reality of medicine that they need to reevaluate their procedures. (c9)

The FDA must change the way drugs are currently approved. The current process is too expensive, limited in scope and of little benefit in clinical practice. (f145)

[T]he FDA needs to get real and allow people who practice medicine do so. (c17)

Our hands are tied enough in medicine. Please don't add more tether. (f74)

Medicine is already bogged down in governmental regulation. (f63)

Regulations are the bane of our practice. (f168)
[O]ne does not want an official, politicized body like the FDA to control the practice of medicine; scientific information should be the basis for decisions made by a free scientific community, not constrained by official sanction. Not infrequently, the "official" view is wrong . . . Physicians, as trained practitioners applying the science of medicine, should have the equivalent of academic freedom. We are adequately constrained by considerations of liability risk and our professionalism. (c18)

Although a significant minority of physicians staked out a consistent position, a majority strongly endorsed the status quo, off-label prescribing but not removal of efficacy requirements. Our reading, however, is that the physician arguments in favor of the status quo do not fully explain the apparent inconsistency between favoring off-label prescribing and favoring efficacy tests on initial uses. Much off-label prescribing is not closely related to on-label prescribing and dropping efficacy requirements would not substantially increase cognitive saturation beyond what occurs today because of already extensive off-label prescribing. The incentive challenge does provide a reason for thinking that the status quo is consistent but in and of itself does not argue against dropping efficacy requirements. Indeed, in recognizing that the suppression effect is too large to justify efficacy requirements for off-patent drugs the incentive challenge raises the possibility that the suppression effect might also be large relative to the benefits of efficacy requirements for new drugs.

**Status Quo Bias**

The fact that a majority of physicians staked out a seemingly inconsistent position in favor of the status quo is not surprising. Status quo bias is natural and common. Samuelson and Zeckhauser (1988), for example, have demonstrated that even the suggestion of a status quo can influence decision making. Thus when respondents were
asked to invest an inheritance from “your great-uncle” in a “moderate risk company, a high risk company, treasury bills or municipal bonds” respondents made one set of choices but when asked to make this choice with the additional information that “A significant portion of this portfolio is invested in a moderate risk company” respondent made quite different choices with a strong bias towards the status quo. (Respondents were told that “The tax and broker commission consequences of any change are insignificant.”)

Most importantly, status quo bias has been shown to significantly reduce the efficacy of decision making in real world settings. Beshears et al. 2006, for example, found that the status quo or default position has a “tremendous” effect on retirement planning. When the default savings rate in one firm’s retirement plan was 3 percent of salary more than a quarter of the workers chose that as their savings rate, despite an employer guarantee of a dollar-for-dollar match on contributions of up to 6 percent of salary. Later the same company switched to a 6 percent default savings rate; in that setting hardly any new workers chose the 3 percent savings contribution rate. Employees could easily switch from one plan to another and had strong incentives to choose the best plan for retirement yet the trivial change in the status quo significantly influenced behavior. We also see seemingly trivial differences in status quo influence important choices in the medical field. It’s well known, for example, that default procedures and standards of care differ across the country and that these defaults are often more determinative of how a patient is treated than more objective factors (Weinstein et al. 2006, Baicker 2004).
Towards a Liberal Consistency?

We have not proven, of course, that physicians are biased towards the status quo nor that the status quo should be changed in favor of a more consistent and liberal position. Nevertheless, it’s important that these questions be investigated because status quo bias in the field of policy towards the FDA could be resulting in unnecessary morbidity and mortality (Peltzman 1973, Wiggins 1981, Grabowski and Vernon 1983, Tollison 1996, see also Klein and Tabarrok 2002 for a review).

It’s also important to understand the arguments for and against the consistent liberal position because significant trends exist which are moving policy in that direction. The FDA’s position on promotion of off-label prescriptions, for example, has liberalized in recent years. After losing a series of court cases (e.g. Washington Legal Foundation v. Friedman 1998, Washington Legal Foundation v. Henney 2000, Pearson v. Shalala 1999, Pearson v. Shalala 2001) the FDA has now accepted that manufacturers of pharmaceuticals and dietary supplements have significant First Amendment freedoms. In the past the FDA forbade dietary supplements from making health claims, such as the benefits of folic acid or aspirin after a second heart attack (e.g. Rubin 1995, Keith 1995). The FDA can longer forbid manufacturers from making health claims, but it can and will grade claims according to their scientific merit. A new grading system will assign letter grades — ranging from "A" to "D" — on each claim a dietary supplement company makes, indicating the quality of the scientific evidence supporting the claim. Competition and advertising on health consequences has had beneficial effects in markets from cereal to cigarettes, so we think this approach is promising (Ippolito and Pappalardo 2002, Calfee 1997).
Pharmaceutical manufacturers now may disseminate off-label information in the form of peer-reviewed journal articles and medical textbooks. Could the new grading system for dietary-supplement claims be extended to off-label uses? That is, does information about non-approved uses need to be “off-label”? A split-label approach would allow manufacturers to present subsequent-use information on the label and in their other media. As with the grading system, the FDA could keep speech and competition within bounds by grading the claims.

More recently the DC Circuit Court of Appeals in Abigail Alliance v. Eschenbach (2006) ruled that dying patients have a due process right to access drugs once they have been through FDA approved safety trials. The FDA's refusal to allow firms to sell and patients to buy these drugs "impinges upon an individual liberty deeply rooted in our Nation's history and tradition of [respecting the right of] self-preservation." The court further noted that off-label prescribing suggests that the FDA’s control over drug approvals is not beyond question:

Government regulation of drugs premised on concern over a new drug’s efficacy, as opposed to its safety, is of recent origin. And even today, a patient may use a drug for unapproved purposes even where the drug may be unsafe or ineffective for the off-label purpose. Despite the FDA’s claims to the contrary, therefore, it cannot be said that government control of access to potentially life-saving medication “is now firmly ingrained in our understanding of the appropriate role of government,”...

VI. Concluding Comments

New drugs must be tested for efficacy before being permitted but no such requirement exists for new uses of old drugs. In a survey of some 500 physicians we found that most physicians favored the status quo, but in our judgment they were not able
to really resolve the inconsistency. The inconsistency could be resolved either by removing FDA requirements on efficacy or by increasing restrictions on off-label prescribing.

In our judgment, this investigation provides support to the reform proposal that would resolve the inconsistency by dropping efficacy requirements, so that people were freer to produce, sell, and market drugs, even for initial uses, with the clearly stated caveat that the drug’s efficacy has not been certified by the FDA. Those with the best knowledge of the particular circumstances and with the strongest incentives to do right by the patient would then have expanded options of utilizing therapies that may be very beneficial to them.
Appendix

*Correlations between Liberalization and Other Variables*

We investigated whether support for liberalization correlated with other variables. Table 1 reports a probit regression for which the dependent variable was 1 if the physician favored making FDA efficacy certification optional and 0 if he opposed that reform. (We dropped respondents answering Don’t know/ Not sure). Independent variables included years of practice, whether the physician worked at a teaching hospital, was a pediatrician, physician career type, and off-label usage. Years in practice, working in a teaching hospital and being a pediatrician had no discernible effect on support for FDA liberalization. The responses to the career question are divided between Strictly Practitioner, Mainly a Practitioner, About Half Practitioner-Half Researcher, and Mainly Researcher. We dropped Strictly Practitioner, so read the coefficients on the other career variables as relative to physicians who are Strictly Practitioners. We find that those who are mainly practitioners are about 5% less likely than strict practitioners to support liberalization, although the effect is not statistically significant. Physicians who report splitting their time evenly between practice and research, however, are 22% less likely than strict practitioners to support liberalization, and those who mainly do research are about 25% less likely, with both coefficients statistically significant at the 1 percent level. One interpretation of the result might be that practicing physicians are more sensible to the heterogeneity of patients’ conditions and in closer contact with the patients who lose out because of FDA restrictions. Hence, practicing physicians are more cognizant of the costs of FDA restrictions and less enamored with the FDA. Another interpretation is that physicians who do research have a stronger allegiance to official

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21 We also dropped respondents if there were missing or not sure answers on the independent variables.
institutions because they are more involved in the world of government determinations and research grants, and feel themselves part of an academic or elite social stewardship.

Table 1: Probit Regression of Support for FDA Liberalization

<table>
<thead>
<tr>
<th>Variable</th>
<th>Marginal Effect</th>
<th>(Standard Error)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td>-0.0003</td>
<td>(0.002)</td>
</tr>
<tr>
<td>Teaching Hospital (Yes=1, No=0)</td>
<td>-0.030</td>
<td>(0.053)</td>
</tr>
<tr>
<td>Pediatrics (Yes=1, No=0)</td>
<td>-0.004</td>
<td>(0.055)</td>
</tr>
<tr>
<td>Mainly a Practitioner</td>
<td>-0.052</td>
<td>(0.054)</td>
</tr>
<tr>
<td>Half Practitioner, Half Researcher</td>
<td>-0.220**</td>
<td>(0.062)**</td>
</tr>
<tr>
<td>Mainly a Researcher</td>
<td>-0.247**</td>
<td>(0.089)**</td>
</tr>
<tr>
<td>Off-Label Usage</td>
<td>0.40*</td>
<td>(0.19)*</td>
</tr>
<tr>
<td>Observations</td>
<td>381</td>
<td></td>
</tr>
</tbody>
</table>

Standard errors in parentheses
* significant at 5%
** significant at 1%

We also find that physicians who report greater off-label prescribing are more likely to support making efficacy standards optional. The coefficient on off-label usage indicates that a 1% increase in reported off-label prescribing increase the probability of supporting FDA reform by 0.40%. Thus an increase of one standard deviation, about 12 percentage points, would raise predicted support for liberalization by just under 5

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22 To run the regression we set off-label use at the means of the respective intervals, thus 10-20% was set at 15% (40% or more was set at 45%).
percentage points. It seems that physicians who regularly prescribe off-label (or, who are aware that they do so) are more likely to embrace private, voluntary forms of efficacy certification.

Table 2 shows support for FDA liberalization by area of specialization (for areas with at least 20 respondents). We find no statistical significance between the rates.

<table>
<thead>
<tr>
<th>Area</th>
<th>Percent Supporting Liberalization</th>
</tr>
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<tbody>
<tr>
<td>Allergy</td>
<td>34.7% [23]</td>
</tr>
<tr>
<td>Cardiology</td>
<td>25.6% [39]</td>
</tr>
<tr>
<td>Internal Medicine</td>
<td>35.2% [122]</td>
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<tr>
<td>Neurology</td>
<td>27.7% [36]</td>
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<tr>
<td>Oncology</td>
<td>36.3% [33]</td>
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<tr>
<td>Pediatrics</td>
<td>31.8% [113]</td>
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REFERENCES


