Do Off-Label Drug Practices Argue Against FDA Efficacy Requirements? Testing an Argument by Structured Conversations with Experts

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By

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Abstract: The Food, Drug and Cosmetics Act of 1938 with amendments in 1962 is inconsistent regarding FDA certification of a drug's efficacy. The act requires efficacy certification for the drug's initial ("on-label") uses, but does not require certification before physicians may prescribe for subsequent ("off-label") uses. Are there good reasons for this inconsistency? 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, and almost all physicians said no. It asked whether the efficacy requirements for initial uses should be *dropped*, and most said no. We then gently challenged respondents asking them whether opposing efficacy requirements in one case but not the other involved an inconsistency. In response to this challenge we received hundreds of written commentaries. This investigation taps the specialized knowledge of hundreds of physicians and organizes their insights into challenges to the consistency argument. Thus, it employs a method of *structured conversations with experts* to test the merit of an argument. Is the consistency argument a case of "foolish consistency," or does it hold up even under scrutiny?

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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. Shapiro (1979) and Tabarrok (2000) argue that this combination of positions, as embodied in the law, is inconsistent. Either FDA efficacy requirements are on-net beneficial, in which case they should apply to all drug uses, or they are not, in which case they should be withdrawn for all drug uses.

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. A significant minority also opposed FDA efficacy requirements on initial uses. But the majority supported the FDA efficacy requirements on initial uses while opposing them for subsequent uses. *Is it inconsistent to favor efficacy requirements for new drugs but not for new uses of old drugs?*

We asked physicians that, too. We asked them 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. We think of our investigation as a less conventional form of scientific testing (see Blinder et al.1998 and Bewley 1999 on using surveys in this manner). If the consistency argument for FDA liberalization has serious weaknesses, physicians (practitioners and researchers) would be in a special position to identify and expose those weaknesses. Better than anyone else, physicians would know the hazards of allowing drugs lacking FDA efficacy certification onto the market. We engaged some 500 experts in structured conversation, bringing their knowledge to bear on the important scientific hypothesis: *Making initial FDA efficacy certification optional would improve social welfare*. Our method should be distinguished from surveys that collect data or merely elicit stated preferences. Our interactive survey asks for justifications. Each "observation" is the generation of a separate conversation. We turn to the doctors, not because they are authorities on the economics of FDA policy, but because they may be in a special position to challenge insightfully the liberalization position that generally emerges from economists' work on the FDA.

II. The Consistency Argument:

If Off-Label Uses Should Not Require FDA Efficacy Certification, Why Should On-Label Uses Require FDA Efficacy Certification?

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. Amoxicillin 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).

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.

Logical consistency does not tell us which of the above two choices is preferable. Tabarrok (2000) argues for the first alternative. FDA requirements might enhance the safety and effectiveness of drugs eventually permitted, but FDA requirements have at least two negative effects. First, they delay the arrival of superior drugs. Second, they increase the costs and uncertainties of bringing a new drug to market; hence, many drugs that would have been developed are not. All the people who would have been helped by these drugs are not. Beginning with Peltzman (1973), many researchers have evaluated these costs and benefits, and to a striking degree reach a consensus that on the margin the FDA regulation is deleterious (for a literature review see Klein and Tabarrok 2002).

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, according to this argument, 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. Physicians learn of off-label uses from medical research and experience conveyed by peer-reviewed publications, newsletters, lecture presentations, conferences, advertising, and conversations with trusted colleagues. The new learning comes from many sources: utilization and outcome reviews, clinical and epidemiological studies, new theories advanced by scientists, new judgments made by professional and scientific bodies, and new results reported by pharmaceutical companies. As the enterprise of medical science proceeds, the new learning flows to the medical practitioners, albeit in fits and starts. Scientists and physicians, working through professional associations and organizations, make official determinations of "best practice" of off-label uses in standard reference compendia such as *AMA Drug Evaluations, American Hospital Formulary Service Drug Information,* and *U.S. Pharmacopoeia Drug Indications*. Tabarrok (2000) points to such professional, science-based listings and determinations as examples of the *nongovernmental, nonmandatory certifications* that could – and perhaps should – replace FDA certification of new drugs.

The difference between the on-label and off-label markets is thus not that the off-label market is "unregulated" but that it is unregulated by the FDA. So far as efficacy is concerned, the off-label market is regulated by the consent of patients and the diverse forms of certification made by physicians and medical institutions.

Shapiro (1979) also recognizes the inconsistency in current practices, 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." Rather than favoring the liberalization of new drugs he argues for tightening restrictions on off-label prescribing. Such a position has also been taken by the FDA,[2] although since 1982 the FDA has focused its efforts on limiting pharmaceutical manufacturers rather than physicians.[3] Figure 1 shows how the principle of consistency gives rise to dual arguments for reform.

[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.

Figure 1:
Dual Consistency Arguments

Should there be FDA efficacy requirements on Initial (On-Label) Uses?	Should there be FDA efficacy requirements on Subsequent (Off-Label) Uses? No	Should there be FDA efficacy requirements on Subsequent (Off-Label) Uses? Yes
No	Consistency Argument for Liberalization (Tabarrok 2000)	Plainly Inconsistent
Yes	The Status Quo	Consistency Argument for Expanding FDA Control (Shapiro 1979)

Our survey put this debate to physicians. Nearly all of the 492 responding physicians opposed placing restrictions on off-label prescribing. But a majority opposed the parallel proposal to liberalize the permitting of new drugs. Thus, most physicians, taking "inconsistent" positions, supported the status quo. After the physician had taken his positions, the consistency argument was presented and the physician was asked to respond in an open-ended format. Most of the "inconsistent" physicians stuck to their guns and offered justifications for their combination of positions.

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 flawed or imperfect. We organize the written responses into separate challenges to the consistency argument (the complete set of responses is available online[4]). We re-examine the consistency argument for liberalization in light of what the physicians said about it.

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 to that question before proceeding to 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.[5] 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,

[4] 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/.
[5] The cost of the HostedWare services was $710 and the cost of the Medical Marketing Services was $3,752.

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 a button called "Begin Survey" which led directly to seven preliminary questions about the respondent's practice.

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

CA	11%	[54]
NY	8%	[40]
TX	7%	[34]
FL	5%	[26]
NC	4%	[22]

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

Minimum	0	[6]
Maximum	48	[2]
Mean	16	
Standard Deviation	11	

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:

Internal Medicine	29%	[142]
Pediatrics	28%	[138]

Cardiology	9%	[46]
Neurology	9%	[44]
Oncology	8%	[38]

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][6]
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]

The preliminary questions indicate that we received responses from a diverse group of physicians.

[6] 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.

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.[7] Thus, we conclude that *virtually all physicians favor being allowed to prescribe off-label*. 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."[8]

Given the overwhelming support among physicians for off-label prescribing it is clear that they will not accept the consistency argument for further FDA control. It does not follow, however, that they will accept the consistency argument for liberalization. Since the argument for further FDA control of off-label prescribing has almost no support, we often refer to the consistency argument for liberalization as simply "the consistency argument."

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[7] 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.

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

> **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? [[9]] 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 physicians were not decidedly in favor of retaining initial efficacy requirements, and 27 percent favored eliminating FDA efficacy requirements. But these numbers are consistent with previous studies. The Competitive Enterprise Institute in Washington, DC, has posed a very similar question in five telephone surveys of physicians conducted by The Polling Company. After asking several questions which do

[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

bring out the costs of drug 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".[10] Our results and those of CEI show 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.

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.

[10] Competitive Enterprise Institute 2002 summarizes all five CEI surveys conducted from 1995 to 2002.

The Consistency Argument

The majority who gave "inconsistent" responses next encountered the following statement and question[11]:

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

[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.

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.]** 76% [50]
> - **I think there's merit to the argument but other considerations explain my responses. [Use other box for further response.]** 20% [13]
> - **It is for other reasons that I have favored allowance in both of my replies; the consistency argument is faulty because [Use other box for further response.]** 5% [3]

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.

[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.

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 those comments with a charitable eye for challenges to the consistency argument for reform.[13] We have organized the comments into a series of three challenges. In presenting a challenge our first responsibility is to set out the idea as the physician respondents themselves would approve; that is, to represent their idea fully and faithfully. We then give a response, the next step on our part in the conversation. In formulating responses we often draw upon the remarks of other physicians. Sometimes we step out of the conversation and offer observations or comments on what the physicians said, to shed light on the character of those comments or to enlarge the context of the conversations. We use sub-headings to separate the various "voices."

[13] The complete set of comments has been put into a compendium available online. Each comment is marked to indicate any relatedness to the challenges. Also, some comments contained no clear theory that we could discern (comments that simply restated positions, justify only one of the positions taken by the respondent, or describe the respondent's own prescription practices).

Before turning to the challenges in detail we set out a conceptual framework that will be useful in understanding and evaluating the challenges.

The "Knowledge Effect" versus the "Suppression Effect"

The physicians challenges point to a good effect and a bad effect of efficacy requirements, whether on initial or subsequent uses. The good effect is that to some degree requirements induce the pharmaceutical company to fund the requisite studies and thereby enhance knowledge beyond the level otherwise attained. Call this the "knowledge effect." "Better knowledge" may mean more information about specific drugs but also includes the eradication or avoidance of spurious and useless ideas. Improving the quality of knowledge in the system is obviously a good thing. Thus one physician wrote that "Without an efficacy study requirement, many studies would never be done and the world would not really know if the drug works." "However," this same physician continued, "those same studies end up costing the US and pharmaceutical [companies] a great deal of money (f42)."

Efficacy requirements increase the costs, delays, and uncertainties involved in developing and getting initial and subsequent indications to legal status.[14] Many physicians noted this consequence of requirements:

> Many well accepted therapies are not FDA approved as there is tremendous cost in time and money to gain approval. (f9)
>
> The time to certify efficacy (by the FDA) is frequently excessive. (g85)
>
> Medical research is generally much ahead of the FDA regulatory process. (g173)

[14] 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.

> To mount a full study and provide the mountain of paperwork required by the FDA to justify a use would markedly limit our armamentarium. (f74)
>
> I don't want to wait until the pharmaceutical company jumps through all of the FDA hoops for each use. (g7)

The costs of gaining FDA approval will in some cases discourage the actors in the entire nexus of medicine from bringing the indication forth. This is the "suppression effect." Efficacy requirements increase the knowledge about the indications that do become available, but suppresses their number.

A tradeoff between knowledge and suppression may accommodate different policy positions in differing cases. Again, most physicians supported initial-use but not subsequent-use efficacy requirements There were two common challenges suggesting why the tradeoff favors efficacy-requirements for initial but not subsequent uses.

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 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 plainly by saying:

> 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.

In terms of the beneficial "knowledge effect" of efficacy requirements, these doctors are saying that the knowledge effect is large for initial uses but, because of the

accretion of knowledge through experience, not so large for subsequent uses. In other words, once a drug is released in its initial use, the further imposition of efficacy requirements for subsequent uses would not be important to advancing knowledge about those subsequent efficacies. Thus, for the subsequent uses the knowledge effect is swamped by the deleterious suppression effect. As noted, the survey respondents resoundingly opposed the imposition of new requirements on off-label prescribing because such requirements would suppress many important uses.

Response to the Relatedness Challenge

Our response to the relatedness argument is usefully contrasted with the FDA's response. Though exercising some judgment and flexibility, the FDA does not put great confidence in the relatedness argument. The FDA does not regard relatedness as anything like a sure thing. Crossing age divisions and going from seasonal to perennial allergic rhinitis may have been reasonable – but sometimes age and seasonality differences do matter which is why the FDA maintains these distinctions. Similarly, a senior associate commmisioner of the FDA criticized the relatedness argument with respect to drug classes by writing that "physicians may assume that all members of the drug class will behave similarly, and prescribe them interchangeably. This assumption, however, may be very risky, because all members of a drug class do not behave identically (Suydam 1999)."

We take a middle ground between that of the physicians and the FDA. The challenging physicians observe that off-label uses are often related to on-label uses and suggest that the gap between related uses and effective uses is easily bridged. The FDA

observes that related drugs do not always have related effects and argues that the gap is too large to be safely bridged absent its own approved clinical trials. But in practice the gap between related indications and effective indications is bridged by a sophisticated process of testing and evaluation involving universities, hospitals, non-profit health foundations, manufacturers, researchers, scientific journals, compendia,and others.

Each newly permitted drug projects a wide range of theoretically related and *possibly* effective off-label indications, and the promise of each gradually diminishes the farther (in terms of current medico-pharmacological understanding) such prospective indications are from the on-label indications. But *being pharmacologically related to the on-label use and actually being effective are two very different things. Ex ante*, the successful extrapolation to *effective* off-label indications is not typically a sure thing.

Medical science explores possibly useful related uses and if those possibilities appear to pan out it adopts them and brings them into professional listings such as the leading formularies and compendia. There are, of course, cases of improper prescribing and consequent suffering.[15] But, generally speaking, medicine does not adopt related (or potentially related) indications that are not effective.

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

[15] See Lazarou, Pomeranz, and Corey 1998 on adverse drug reactions in hospital patients.

related to – were not direct or certain extrapolations from the on-label uses. Related uses are transformed into off-label uses through a decentralized process of medical evaluation.

Further Response to the Relatedness Challenge

In many cases, the off-label use is *not* significantly related to the on-label use. 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. The consistency argument asks, 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?

The role of serendipity in discovering off-label uses also testifies 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 under the brand name Rogaine as a treatment for baldness.

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). Another 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)

Finally, "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 alcoholism (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.

Side Comment on Relatedness and Drug Permitting

Studies of the FDA's counterparts in the U.K. and Spain find those drug-permitting agencies to be as effective as the FDA in screening out unsafe drugs (Bakke, Wardell, and Lasagna 1984, Bakke et al 1995). The relatedness challenge, therefore, does suggest FDA reform in another direction. If doctors should be allowed to prescribe across age populations or other "closely related" groups then shouldn't doctors be

allowed to cross national populations? A drug's pharmacological mechanisms in British patients are extremely closely related to its mechanisms in American patients. The relatedness challenge, then, bolsters the case for having the FDA automatically permit any drug that has been legal permitted in Canada, Australia, Britain, Spain, Sweden, – or whatever set of countries are deemed to have sound permitting agencies. This proposal is sometimes referred to as "reciprocity," though the logic holds even if automatic approval is only one-way. The proposal has not to our knowledge been included in a survey of physicians; it would be interesting to see how physicians who favor FDA efficacy requirements respond to this line of argument.

B. ***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.

Numerous 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.) 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).[16] The balance of the knowledge effect and the suppression effect , these physicans 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.

Response to the Incentive Challenge

We agree that 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.[17] Thus the fact that patent is winding down is a good argument in favor of not requiring FDA efficacy-certification for off-label prescriptions.

[16] Other challenges along these lines are g20, g40, g58, g59, g79, g104, g115, g121, and g134.
[17] 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).

The incentive challenge maintains that, by and large, patents are a necessary *but not sufficient* inducement for producing efficacy studies — to create sufficiency we need FDA efficacy requirements. One of the physicians who favored liberalization responded 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 (or, at least not for very long) without professional, credible demonstration of its efficacy. 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 credibly 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, and the off-label experience illuminates the prospective world in which initial efficacy requirements are optional. 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. The FDA has a monopoly on drug permitting, but not on

drug-use certifying. Here are some physicians remarkson 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)

Some of the physicians recognized the importance and validity of the decentralized testing process that certifies off-label uses yet they also revealed an allegiance to status-quo FDA procedure. Consider the following complete remark:

> 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. To allow any drug that has shown it is not toxic to be used for anything is bad science and bad policy. (g64)

The last sentence strikes us a *non sequitur*. The whole would make more sense if the last sentence read: *Medical science can establish and certify efficacy, and thereby minimizing ineffective therapy, without the FDA.* We think that many doctors overestimate the knowledge effect of efficacy requirements because they underestimate medicine's ability to weed out ineffective indications.

Further Response: How large is the suppresion effect?

The off-label experience testifies to the fact 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. Let us accept, however, that if initial efficacy requirements were dropped, there would be a decline in knowledge about new drugs. However large the decline in knowledge might be, what matters in the final analysis is how it compares to the suppression effect. The survey responses resoundingly recognized that requiring FDA efficacy certification for subsequent indications would greatly suppress those uses. The physicians likely understand, therefore, that efficacy requirements on initial uses also suppress drug development. The issue of patents can obscure this point. The patent prospect induces *some* firms to produce *some* new drugs

despite very high FDA certification costs. But higher costs means fewer new drugs. Some suppression occurs.

Physicians are aware of the suppression effect with regard to drugs available in other countries. Thus one physician commented:

> The FDA has already by its slowness kept us behind by several generations of new therapeutics. In Seattle, we have the opportunity to sometimes send patients to Canada to get medications that are unavailable in the U.S. (c187)

But the suppression effect probably goes far beyond the benchmark of the union of Canada's, Europe's and America's pharmacopoeias. Even more serious than the suppression of drugs available in other countries is the suppression of drug development. Sam Peltzman (1973) addressed the suppression effect of the 1962 Kefauver-Harris which added a proof-of-efficacy requirement to the existing proof-of-safety requirement, removed time constraints on the FDA disposition of NDAs, and gave the FDA extensive powers over the clinical testing procedures drug companies used to support their applications. Using data from 1948 to 1962, Peltzman created a statistical model to predict the yearly number of new drug introductions. Despite the model's simplicity, it tracks the actual number of new drug introductions quite well, as indicated by figure 1.

{ HYPERLINK "http://www.fdareview.org/graphics/PetzmanChart.gif" **}**

> Figure 1: According to Peltzman's empirical research, the requirements imposed in 1962 significantly suppress the development of new drugs.

Because Peltzman's model tracks the pre-1962 drug market quite well, we have some confidence that *if all else had remained equal*, the model also should have roughly tracked the post-1962 drug market. Peltzman's model, in other words, estimates the number of new drugs that would have been produced if the FDA's powers had not been increased in 1962. Thus, by comparing the model results with the *actual* number of new drugs, we can draw an estimate of the effect of the 1962 amendments. The model predicts a probable post-1962 average of 41 new chemical entities (NCEs, or new drugs) approved per year, yet in fact the average was only 16. The 1962 Amendments appear to be responsible for a 60 percent reduction in the number of new drugs. The average number of new drugs introduced pre-1962 (40) was also much larger than the post-1962 average (16). Thus, whether one compares pre- and post-1962 averages or compares the results from a forecast with the actual results, the conclusions are the same: the 1962 Amendments caused a significant drop in the introduction of new drugs.[18] Using data of longer span, Wiggins (1981) also found that increased FDA regulations raised costs and reduced the number of new drugs by approximately 60 percent.

Furthermore, we must recognize a difference in *correction dynamics*. When the FDA is stingy in giving permission, or when efficacy requirements simply make certain lines of investigation uneconomic, drug development is stunted, and there is no reliable correction mechanism. The FDA can easily suppress a drug that could have saved tens of

[18] Since 1962 marked not only the introduction of efficacy requirements but also of other new requirements, the measured impact of the 1962 amendments cannot be taken to be an exact measurement of the "suppression effect" as meant here. Yet it is well-known that proof-of-efficacy was the most significant amendment in 1962, and that getting the FDA to "sign off" on efficacy is much more expensive, prolonged, and uncertain than getting it to "sign off" on safety, so there is good reason to take Peltzman's measurement as demonstrating that the suppression effect on new drugs is large.

thousands of lives with little hint of controversy or even acknowledgment. This is quite unlike the correction that tends to occur when ineffective and unsafe drugs are released onto the market.

Thus the suppression effect appears to be very large and this must be weighed in the balance when considering the loss of knowledge caused by making initial efficacy requirements voluntary.

C. *The 'flooding the market with ineffective drugs' challenge*

Dropping efficacy requirements would flood the market with ineffective drugs; pharmaceutical companies would promote ineffective drugs and push them on patients and doctors.

In a freer system drug manufactures and others would still have significant incentives to seek efficacy-certification of new drugs. Yet the number of ineffective drugs on the market will also increase. FDA regulation suppresses ineffective drugs even more than effective drugs. Many of the anti-liberalizers wrote vehemently against "flooding" of the market with ineffective drugs.[19] "[T]hat's what the makers of Aspercreme and Icy Hot are for!" (g87). Several made reference to the "chaos" of dietary supplement or herbal remedies (e.g., g29, g69, g73).

[19] 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).

Response to the flooding challenge

The absolute number of ineffective drugs is a poor guide to the cost of such drugs in the medical system because drug use is filtered by medicine. If the filter works well, then society could gain even if many more ineffective drugs are matched by only a handful of additional effective drugs. The ineffective drugs will be prescribed rarely while the effective drugs will be saving lives.[20] Some physicians, however, questioned the efficacy of the filtering process.

> [I]t 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)
>
> [P]hysicians sometimes give in to patient requests for medications even though they may not think that the drug is effective. (g119)
>
> [P]hysicians 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)

[20] We hypothesize that ineffective drugs are more likely to be resorted to when the opportunity cost of such usage is low. In particular, we suggest that ineffective drugs will be prescribed/used more often the safer they are and the fewer are effective alternatives. Today, we see many questionable but relatively safe drugs being sold to treat sleeplessness, joint pain and memory problems (these drugs are often also sold OTC, without the filtering mechanism of prescriptions - but see Peltzman 1987 on prescriptions). The costs of such questionable usage, however, is probably low. Also, in cases of deadly and incurable conditions, doctors and patients sometimes resort to off-label and quite possibly ineffective prescriptions after conventional treatments have failed. But the added hope, as well as experimentation, of the off-label system is in this case a benefit, not a cost.

But this fear of a flooding of the market 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?

Despite this apparent inconsistency the comments of those physicians who questioned the efficacy of the filtering mechanism do suggest important questions: How well does medicine filter out ineffective drugs? And, how well would the filter have to work such that under liberalization the gain in the number of effective drugs would compensate for a higher tide of ineffective drugs? Answering these questions is a good line for further research.

Some respondents did provide a possible resolution of the inconsistency between fear of flooding and support of off-label prescribing as they spoke of a flood of new drugs *that would be heavily promoted*. Thus, respondents wrote:

> 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)

Responses to the promotion challenge

The promotion challenge calls for two responses. First, 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.

A second response would meet these respondents head-on, arguing that it would be a *good* thing, under the only-safety-requirements proposal, to grant pharmaceutical companies freedoms of speech like those enjoyed today in promoting on-label uses. We will not pursue that line of argumentation, but merely note that a substantial body of scholarly 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 (Leffler 1981; Ippolitio and Mathios 1991, 1995; Ippolito and Pappalardo 2002; Masson and Rubin 1985; Rubin 1994, 1995; Keith 1995, Calfee 1997, Tabarrok 2000).

D. Brief Treatment of Other Challenges

Many physicians rebutted the consistency argument by saying "efficacy requirements make drugs safer" (r70). Phase I and other parts of the FDA process

specifically oriented toward safety provide what may be called s^1 level of general safety knowledge or assurance, while the full set of FDA requirements, including those geared toward efficacy, provide a higher or extended level s^x. The challenge would seem to maintain that the higher level of safety assurance s^x ought to be required, and that therefore the current "efficacy" requirements ought to be retained. We feel that this response does not deflect the thrust of the consistency argument. Even if one were to grant that the FDA ought to require s^x, there would be no reason to achieve that by testing for efficacy in one particular use. And if the FDA implemented requirements explicitly formulated for ensuring the higher level of safety, then any remaining efficacy requirements would be open to challenge by the consistency argument.

It's revealing that the physicians did not make one argument that is common in the literature. Shapiro (1979) and Christopher (1993) both hold that imposing efficacy requirements on subsequent uses would be desirable but they recognize that such requiremenets would be intrusive and difficult to enforce and for that reason it could be (second) best to allow off-label prescribing. None of the physicians made this argument. Virtually all the doctors in the survey would join us in saying that the debate is over whether to drop efficacy requirements on initial uses, not whether to impose them on subsequent uses.

V. Physicians Endorse Liberalization and the Consistency Argument

We have focused on the status-quo respondents and their challenges. This may give a misleading account of the support for the consistency argument for reform. Recall, that *32 percent of those physicians 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)

VI. Concluding Comments

Is the consistency challenge to initial efficacy requirements foolish? To address that question, this investigation goes beyond mere precept, anecdote, and individual opinion. It taps the working knowledge of hundreds of physicians and organizes their insights and interpretations into a number of carefully formulated challenges to the consistency argument. We have called the investigation a form of scientific testing. What, then, are the test results?

The investigation make clear that liberalization proponents cannot wield the consistency argument as though it were a broadsword that cuts by clean logic through the status-quo efficacy requirements. The expert "local" knowledge of some 500 physicians has pointed to complications in the argument but, in our judgment, has not produced a strong rebuttal. Many of the comments of the 500 physicians supported the consistency argument for FDA liberalization. But important, complex issues like FDA policy always involve broad-gauge issues of interpretation and even of the proper vision of the polity, so others' judgments may differ from our own. Hence we have striven to render our arguments and those of the dissenting and concurring physicians as clearly as possible.

The off-label market provides a window onto how a less regulated drug certification system would operate, but the physician comments raise many important questions for future research. How related are off-label to on-label uses? How should relatedness be assessed? When an off-label use is unrelated, how is that use certified? How quickly does the process work? How do these processes compare with the FDA? Is

there a lot of off-label usage that is ineffective? To what extent does medicine filter out ineffective uses when superior therapies are available? In safety and effectiveness, how do off-label compare to on-label uses?

Little research on off-label prescribing has been done. In drawing attention to the consistency argument and its challenges, we hope to shed light on off-label prescribing and its significance in the comparative analysis of regulatory institutions.

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).[21] 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

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

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

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 %.[22] Thus an increase of one standard deviation, about 12 percentage points, would raise predicted support for liberalization by just under 5

[21] We also dropped respondents if there were missing or not sure answers on the independent variables.
[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 2: Percent of Physicians Who Support Making FDA Efficacy Certification Optional, by Area of Specialization

Area	Percent Supporting Liberalization
Allergy	34.7% [23]
Cardiology	25.6% [39]
Internal Medicine	35.2% [122]
Neurology	27.7% [36]
Oncology	36.3% [33]
Pediatrics	31.8% [113]

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