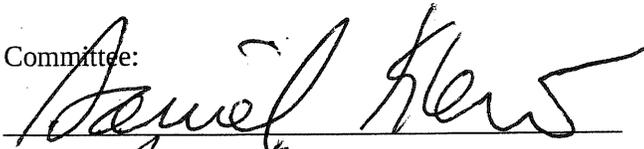


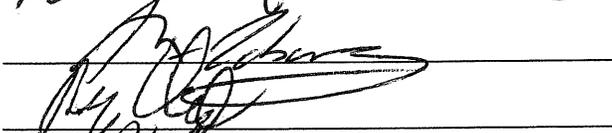
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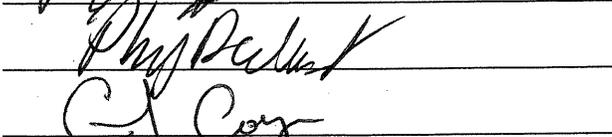
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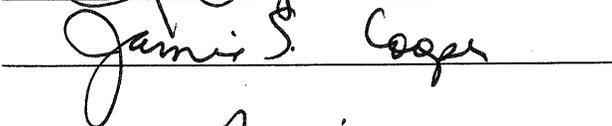
Jason Briggeman
A Dissertation
Submitted to the
Graduate Faculty
of
George Mason University
in Partial Fulfillment of
The Requirements for the Degree
of
Doctor of Philosophy
Economics

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Spring Semester 2015
George Mason University
Fairfax, VA

Searching for Justification of the Policy of Pre-Market Approval of Pharmaceuticals

A Dissertation submitted in partial fulfillment of the requirements for the degree of
Doctor of Philosophy at George Mason University

By

Jason Briggeman
Master of Arts
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Spring Semester 2015
George Mason University
Fairfax, VA

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DEDICATION

in loving memory of my brother Nathan

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TABLE OF CONTENTS

	Page
List of tables.....	vii
Abstract.....	viii
Introduction.....	1
Engagement with K&B survey responses supporting pre-market approval	22
Kenneth Arrow	22
Pedro Pita Barros	50
Cornelis Boersma.....	62
Don Husereau.....	76
Randall P. Ellis.....	106
Marc L. Berger.....	111
John E. Brazier.....	119
Anthony John Culyer	128
F. M. Scherer.....	133
John Hutton.....	139
C. Daniel Mullins.....	147
Nikos Maniadakis	152
Karl A. Matuszewski	158
G�rard de Pouvourville	164
Synthesis of K&B survey responses supporting pre-market approval	167
Key formulations or arguments for pre-market approval	168
Doctors misplace their trust	168
Knowledge is too expensive to communicate to doctors.....	174
Prohibition is benign	175
Phantom validation	177
The regulator is evidently excellent.....	178
The individual and the nation are the only meaningful units of analysis	179
Few appeals to authority	180
A reasonably distinguished group.....	182
Engagement with literature on market failures related to pre-market approval	184

Sam Peltzman (1974).....	185
Fiona Scott Morton and Margaret Kyle (2011)	192
Marc Law (2004; 2011)	200
Daniel Carpenter (2010; 2009c); Daniel Carpenter, Justin Grimmer, and Eric Lomazoff (2010)	206
Uwe Reinhardt (2007).....	229
Tomas Philipson and Eric Sun (2008)	233
Anup Malani and Tomas Philipson (2012).....	237
Patricia Danzon (2011); Patricia Danzon and Eric Keuffel (2014)	244
Eric Posner and Glen Weyl (2013)	255
Jerome Rothenberg (1993).....	263
Carolyn Hughes Tuohy and Sherry Glied (2011)	267
F. M. Scherer (2000).....	269
Charles Phelps (2012).....	272
Robin Hanson (2003; 2008).....	275
Thomas Getzen (2010).....	280
Sherman Folland, Allen Goodman, and Miron Stano (2007).....	283
Synthesis of literature on market failures related to pre-market approval.....	285
Key formulation or argument: There is potential for disaster.....	286
Key formulation or argument: Producers bear insufficient liability.....	287
Conclusion.....	289
Study the informational effects, including those on consumer confidence, of product bans	292
Study the safety-efficacy distinction to see if it can form a plausible basis for liberalization.....	293
Study the nature of demand for drugs about which little is known	294
Study the ‘line-drawing’ problem.....	295
Final remarks	295
Appendix A.....	299
Appendix B.....	302
References.....	313

LIST OF TABLES

Table	Page
Table 1. Four policy regimes.....	38
Table 2. Effect of intervention on patient's welfare.....	52
Table 3. Effect of restrictive intervention on patient's welfare.....	53
Table 4. The strongest answers in response to question 12b from those economists who in question 9b say that doctors do not systematically err.....	169
Table 5. Responses from three of the economists listed in Table 4 to question 23b	174

ABSTRACT

SEARCHING FOR JUSTIFICATION OF THE POLICY OF PRE-MARKET APPROVAL OF PHARMACEUTICALS

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George Mason University, 2015

Dissertation Director: Dr. Daniel Klein

In the United States and most other wealthy nations, all drugs are banned unless individually permitted. This policy, called pre-market approval, is controversial among economists; the preponderance of the economics literature that offers a judgment on pre-market approval is critical of the policy, but surveys of U.S. economists show that many, perhaps a majority, support pre-market approval. Here I analyze the results of a recent survey that asked economists who support pre-market approval to justify, with reference to the economic concept of market failure, their support of the policy. I find that, while almost all the economists surveyed could point to a market failure or failures that may plausibly exist and affect the market for pharmaceuticals, none were able to make a well reasoned connection between those market failures and the particular remedy of pre-market approval. None of the economists surveyed cited in support of their position any literature specific to pre-market approval. I supplement the survey findings with a review

of relevant reading material assigned in health economics courses at top universities, searching that material for discussions of what may justify pre-market approval. I find a strong argument that the prospect of overt disasters being caused by avoidable mistakes can justify some intervention in pharmaceuticals; however, I find little to justify the other interventions that are part of pre-market approval. I suggest that future inquiry into possibilities for liberalizing reform concentrate on understanding matters such as the informational effects of product bans, the distinction between safety and efficacy, the nature of demand for drugs about which little is known, and the political economy of drug substitutes.

INTRODUCTION

Among the higher purposes of economics is to delineate actions or roles that the modern state should and should not take on. Over generations, economists have produced a massive discourse toward such purpose. To join and participate in this discourse today, as an economist, is to have learned and bought into ideas or modes of thought that have become fundamental to the discourse. Specifically, economists writing on the role of the state might be said to agree both on a presumption or starting point for the discourse and on the acceptable forms of argumentation that participants in the discourse may bring to bear.

The starting point for the economists' discourse on the role of the state can be traced at least to Adam Smith. Smith put forward "a strong presumption against government activity beyond its fundamental duties of protection against its foreign foes and maintenance of justice" (Viner 1927, 219). A presumption in favor of a principle places the burden of proof on those who propose contravention of the principle, as the presumption of innocence places the burden of proof on the prosecution. Smith illustrated the presumption by placing two broad rationales for government action in tension with one another, e.g.,

To hinder, besides, the farmer from sending his goods at all times to the best market is evidently to sacrifice **the ordinary laws of justice to an idea of public utility**, to a sort of reasons of state; an act of legislative authority which ought to be exercised only, which can be pardoned only in cases of the most urgent necessity. (Smith 1976/1776, 539, emphases are mine)

Smith's "system of natural liberty"—being devoid of "extraordinary encouragements" and "extraordinary restraints" to any "particular species of industry" (ibid., 687)—is essentially equivalent to contemporary economists' notion of 'the market' (or 'free markets'). Economists implement Smith's presumption for liberty by requiring justification of 'interventions,' i.e., governmental actions aimed at effecting some broad alteration to the market. Interventions are those instances when "the ordinary laws of justice" are sacrificed to "an idea of public utility."

The system of natural liberty is not tantamount to anarchy; Smith explained that, within the system, "three duties of great importance" attach to government. Furthermore, while the first two of these duties were national defense and the administration of justice, the third was that the sovereign is charged with

...erecting and maintaining certain public works and certain public institutions which it can never be for the interest of any individual, or

small number of individuals, to erect and maintain; because the profit could never repay the expence to any individual or small number of individuals, though it may frequently do much more than repay it to a great society. (Smith 1976/1776, 687)

So Smith allowed that provision of certain public goods was within the scope of the system of natural liberty. Furthermore, Smith did not intend for us to view the system of natural liberty as an ideal system; he himself advocated some interventions. The system of natural liberty is valuable because it is “obvious and simple” (ibid.) and therefore can serve as a benchmark or vantage point—a starting point for discourse, as I described it above. Even so, the system does not give us a precise line between ‘the market’ and interventions. What it offers is more the ability to say: some government actions are clearly not interventions, some are hazy, and some government actions are clearly interventions.

In the economists’ discourse, the acceptable forms of argumentation that may be brought forward to justify an intervention are variations on the theme of ‘market failure.’ A claim of market failure is, essentially, a claim that Smith’s “system of natural liberty” must fail in some substantial and particular way to bring about good results, though here *good* can mean either comparatively better or notionally ideal. Sometimes, an economist’s talk of market failure implies she has attempted an analysis in comparative systems: the market is said to fail because it is deemed not as good as some alternate

arrangement, viz., a system that incorporates remedial interventions. But economists are also apt to use ‘market failure’ to denote the failure of the market to achieve certain perfections that are given meaning by a model, metaphor, or allegory. In the latter usage, the failure is more fairly described as absolute than relative, and therefore it does not equate to a case for intervention. This latter usage is the one in play when an economist says that the existence of multiple market failures lead him to advocate the acceptance of a “second-best” scenario (Lipsey and Lancaster 1956). This usage is also generally in play whenever an economist speaks both of market failure and of ‘government failure,’ the latter consisting of substantial and particular ways in which interventionist systems fail to bring about ideal results.

An economist’s judgment on the desirability of an intervention, then, should be consonant with her views on the relevant market failures. An intervention can only be judged desirable if either:

- (1) the market is said to fail relative to that alternate arrangement where the intervention has been imposed, or
- (2) the market is said to fail because it does not achieve certain perfections *and* the intervention is expected to bring the market closer to those perfections.

Unsurprisingly, yet importantly, under both of these standards the effects of the intervention itself are part of the rationale. This is merely an operationalization of the idea that pointing out an imperfection in some state of affairs does not prove it is possible to reach a superior state of affairs (Demsetz 1969). A judgment in favor of an

intervention therefore should be founded upon supporting argumentation that the intervention itself—viz., the policy being proposed as a remedy to the market failure—does lead to outcomes that are preferable to the situation where the intervention is not put in place.

On the foregoing reasoning, each extant intervention should be strongly connected, by economic argumentation and evidence, to one or more market failures. Consider, say, the suggestion that we should treat as justified a complete embargo on imports simply on the presumably true ground that American consumers are on average likely to know more about goods produced at a lesser physical distance from them than they know about the sources of goods produced further away. Such a suggestion should be tentatively rejected by the upholder of the presumption for liberty, who should immediately raise questions such as: What do we know about the magnitude of the knowledge difference? About the magnitude of the resulting costs (if any)? Who bears those costs? By how much would a complete embargo reduce or eliminate those costs? Does a complete embargo have other costs? What are the magnitudes of those costs and who bears them? What alternatives to a complete embargo are there? Does alternative #1 also reduce or eliminate the costs of the knowledge difference? Does alternative #1 have other costs? What are the magnitudes of those costs and who bears them? And on to alternative #2, and on and on. The demanding of such a robust chain of argumentation and evidence is the distinctively ‘economic’ method of contesting the implementation of sweeping interventions on flimsy grounds.

The requirement of a strong connection between an intervention and underlying market failure(s) does not mean that all proposed interventions must founder in the face of an endless stream of demands for evidence and comparisons against alternatives. It *does* mean that when contemplating a potential source of market failure, one should begin one's consideration of possible remedial interventions with candidates such as: (1) the narrowest imaginable intervention that could plausibly redeem the failure and (2) the narrowest of whichever imaginable interventions are aimed at *directly undoing* the source of market failure. For if the narrowest imaginable intervention suffices to treat the failure, then no further search for superior alternate interventions is particularly necessary, at least for the time being (perhaps, in the future, as-yet-unimagined narrower forms of intervention could be evaluated). And the economic analysis of interventions that are aimed at directly undoing the source of market failure should be easier to conduct and communicate, and thus should be more convincing to audiences, than would be the analysis of interventions that do not directly address the market failure and as such almost surely require more extensive reasoning or evidence. So in the example where the potential source of market failure is that consumer knowledge of goods produced nearby is on average greater than that of goods produced far away, the first remediating interventions one should contemplate are those which, in the least obtrusive or costly fashions that one imagines to still be effective, aim directly at closing that gap (Magat and Viscusi 1992, 4). In my own imagination, the most obvious such intervention is the supplying of knowledge to consumers in those instances where such additional

knowledge would most effectively reduce the relevant costs. It may be, of course, that one finds reasons that this intervention will not be worth implementing. But then one moves to an alternative that is less narrow or is aimed less directly at undoing the source of market failure.

In developing a judgment on alternative policies, even though the alternatives as they might be implemented in reality cannot be fully depicted or understood, one does roughly envisage or sketch their shapes and imagine oneself as being in position to choose among the sketched versions. One cannot quantify precisely the costs and benefits of the different sketches (Klein 2008, 339-342), most certainly not when the sketched institutions are very different from those prevailing under the status quo, but still a considered choice must involve the identification and weighing of pros and cons (Tullock 1995). A productive debate can ensue once rival parties achieve some concurrence on basic truths (or facts, insights, formulations) surrounding an issue and have assembled those basic truths so as to assess the central tradeoffs, i.e., the pros and cons that weigh most heavily. While there is no definitive and complete formulation of truths and tradeoffs, a good policy analyst surely aspires to gain a firmer and more intelligent (or powerful, enlightened, persuasive) handle on the issue.

The preceding is an explanation of how an economist may aspire to think about market failure and government intervention, but it is of course not a description of the way in which government interventions actually come to pass. The economist, trained in

the above method, confronts the political environment of status-quo interventions, the historical causes of which are perhaps murky at best. Some economists may feel able and free to challenge, and possibly validate, the status-quo interventions with their findings using the ‘economic’ method (Klein 2012a). Some economists may feel constrained by politics or personal commitments; for example, they may believe that the ‘economic’ method provides the best policy ideas, yet they are concerned that their giving voice to some particular conclusion would undermine broader political values or reduce their own effectiveness in influencing events. And some may see the ‘economic’ method described above as importantly insufficient in some way that eludes explicit explanation; for example, they may presume there is some unarticulated wisdom in the political process that generated the status-quo interventions. Potentially, such non- or extra-economic thinking is partially valid and the ‘economic’ conclusion is in fact inadequate in some respect. But the aspiration to this ‘economic’ approach gives us a benchmark against which we can try to identify and discuss such departures. The ‘economic’ approach is in this way perhaps not unlike Smith’s system of natural liberty, which again is not an ideal system but which being “simple and obvious” gives the analyst a starting point for extended discourse.

* * * * *

The Food and Drug Administration has a charge from the U.S. Congress to impose certain interventions in or on the pharmaceutical industry. One of these

interventions is of a form widely regarded as unique to the pharmaceutical industry: Drugs are banned unless individually permitted, and to gain such permission a new drug must be judged by the FDA to be “safe and effective.”¹ I will refer to this intervention as *pre-market approval*.² Pre-market approval has several components: compulsory testing of new drugs, judgment by the FDA on the drug’s safety and efficacy, and FDA refusal to approve any drug it deems unsafe or ineffective—all taking place prior to product entry into the market, viz., any use of the drug in ordinary medical practice outside of the testing process.

Economists are divided in their views on pre-market approval. William L. Davis and collaborators (2011) asked a random sample of U.S. economics professors their opinion on the possibility of *tighter* requirements for the permitting of new pharmaceuticals and medical devices; 44% of those expressing an opinion said they were opposed, but 26% were supportive and 30% neutral toward a tightening of the current regime. One can draw from Davis et al. (2011) the inference that a majority of economists would oppose liberalizing reforms to pre-market approval (see also Klein and

¹ This short definition of pre-market approval may evoke the image of an evaluator considering a set of known drugs and then banning a subset of those drugs, which in the context of new drugs is misleading. Every new drug is banned unless some party has stepped forward to obtain government approval on its behalf.

² Throughout, my use of the term “pre-market approval” should be understood as denoting *that specific intervention administered by the FDA in the pharmaceutical market*, and not to denote a general category or form of government intervention. In the few instances I speak about such a general category, I use different wording or phrasing. Carpenter, Grimmer, and Lomazoff (2010) use the term “approval regulation” to denote such a general category.

Stern 2007, 317). However, Daniel Klein (2008) searched the economics literature to find argumentation in support of that majority's position; finding little, Klein concluded that "there is not and never was a market-failure rationale" for pre-market approval (ibid., 343).³ Searching the literature more generally, Anup Malani and Tomas Philipson (2012, 101) find that "economists have conducted relatively little theoretical or empirical research on the efficiency of FDA policies. Ironically, if a product application were presented to the FDA with the scant amount of evidence that currently exists on the efficiency of the policies of the agency itself, such an application would likely be rejected on the basis of insufficient evidence."

Despite the division in opinion among economists and the limited support in the economics literature for the majority position, I hesitate to describe pre-market approval as a matter of *controversy* among economists. Sam Peltzman (1973; see also 1974) published in the *Journal of Political Economy* an analysis of the costs and benefits of pre-market approval, but forty years later no other overall evaluation of pre-market approval has achieved comparable recognition in the economists' discourse.⁴ Skepticism of pre-

³ Nardinelli (2014) asserts that "[t]here is no in-house FDA analysis or stance on the market failure associated with the Food Drug & Cosmetic Act's provisions for FDA premarket approval of new drugs and devices."

⁴ Danzon and Keuffel (2007, 22) described Peltzman's *JPE* article as "the only significant attempt to weigh both the benefits and costs of the 1962 Amendments." Malani and Philipson (2012, 127) write: "The final parameters required to evaluate FDA policies are consumer and producer surplus. Only three papers have attempted to estimate these parameters." These three papers are Peltzman (1973), Philipson et al. (2008), and Philipson et al. (2012), the latter two of which do not study "the effect of the 1962

market approval is still voiced by economists, even sometimes in reference materials (e.g., Scherer 2000, 1314-1316), though rarely in top journals (an exception is Philipson and Sun 2008).

The absence of an active controversy among economists over pre-market approval *per se* does not render the matter politically irrelevant. The perceived success of an intervention can lead to calls for a regulating agency's powers to be further augmented (Carpenter 2010). Also, several analysts have suggested that pre-market approval can serve as a model for regulation in other industries, notably financial services (Bar-Gill and Warren 2008; Carpenter 2009a; 2009b; Omarova 2012; Posner and Weyl 2013; Morgenson 2012).

The present dissertation is an expansive effort to collate, synthesize, and evaluate the market-failure justifications that economists have offered for pre-market approval. I examine justifications as they 'exist' at three levels of the economists' discourse. The first level is the justifications that health economists who support pre-market approval offer when asked to explain their position, as represented by the survey responses collected by Klein and Briggeman (2010). The second level is the justifications that have achieved prominence in the health economics literature, including reading material assigned to students attending top university programs in health economics. The third

amendments" but instead "focus on...identifying the value of accelerated introduction of drugs" (Malani and Philipson 2012, 129).

level is justifications that are less prominent in the literature; I make no systematic effort to collect these, but I discuss those of which I have become aware.

Why bother with the survey approach, in addition to a literature review? Two main reasons: (1) the paucity of relevant literature, and (2) to ensure that the views of supporters of pre-market approval are represented, given the finding of Klein (2008) that much of the literature that does exist has been written by opponents of pre-market approval.

Given the disjunction between the economic literature on pre-market approval and the policy views of economists on the same, it could be argued that unacknowledged ideological sensibilities are warping the professional discourse and, perhaps, public policy. Klein and Briggeman (2010, hereafter K&B), using the tools of survey research and admitting to the classical liberal impetus behind their project, sought to excavate this disjunction. K&B did so by calling 305 economists to complete an online questionnaire, asking respondents to justify with economic reasoning their views on pre-market approval. They attempted to assemble a list of “those with expertise and leadership in health economics, research publications on the FDA, leadership in the cultural ecology of professional economics, and eminence in topics of information, uncertainty, and regulation” (K&B 104). Among the 305 invitees were all of the economists among the editorial boards of several leading health-economics journals, as well as all economists previously found by Klein (2008) to have published a judgment on pre-market approval.

The K&B questionnaire listed common categories of market failure and inquired as to whether the respondent believed that any species of each type of failure applied to the market for pharmaceuticals. The questionnaire also proposed several partial liberalizations of the pre-market approval regime and asked whether the economist would support each proposal. Whenever a respondent indicated belief in a market failure or opposition to a liberalization proposal, he or she was asked to elaborate with an open-ended response. In keeping both with the economics tradition that intervention requires justification and with their purpose of locating a coherent market-failure justification for pre-market approval, K&B did not probe denials of market failure or statements in support of liberalization. Unconventionally, K&B required that respondents allow their names to be published along with their responses.

Briggeman, Klein, and Kevin Rollins (2010a) fulfill the commitment made by K&B to publish complete transcripts of each response to the K&B survey, with no critical commentary appended, in *Econ Journal Watch*. K&B received survey responses from forty-four economists, including Kenneth Arrow, William Comanor, David Dranove, Sam Peltzman, Paul Rubin, and F. M. Scherer. As reported in a short article summarizing responses to the closed-end questions in the survey (Briggeman, Klein, and Rollins 2010b), a narrow majority of the responding economists said that they support the U.S. policy requiring pre-market approval of new pharmaceuticals and devices, with the minority neutral or opposed to the policy. Over two-thirds of the responding economists

said there is a sound market-failure rationale for the policy; most of these said that imperfect information or public-goods aspects of knowledge are a source of market failure.

The present paper evaluates the responses to the K&B questionnaire given by each of the 14 study participants who support the policy requiring pre-market approval of new pharmaceuticals and devices, believe there is a sound market-failure rationale for pre-market approval, and elaborated on such belief at some length in response to the open-ended questions posed by K&B. In the section immediately below, I attempt to enter into each respondent's reasoning and to aggressively engage that reasoning as a critic. I adopt the perspective that I associate above with the economists' discourse: I hold to a presumption of liberty and place the burden of proof on the respondent, who upholds the intervention. But I urge the reader not to interpret what follows as a series of debates. The participants in the K&B study were uncompensated, and further, they were assured that *Econ Journal Watch* would not publish any criticism of their responses. So there is no reason at all to think that any of the respondents put forward nearly as strong a case as they are capable of making. But in what follows I write, aggressively, as if each respondent had made as full a case as possible. Where I find a respondent's argument to be importantly incomplete, I say so. Where I find a lack of evidence to support a respondent's claim, I ask: Where is the evidence?⁵ I am certain that, in a debate between

⁵ Respondents to the K&B questionnaire were expressly prompted or invited to provide "evidence" several times (questions 7a/8b, 9a/10b, and 33).

me and a respondent, the respondent could capably rebut my adopted position and defend their own, and that often the respondent could extend an importantly incomplete argument or could provide evidence where it had been lacking. My goal is not to ‘win’ anything, but to *locate* the *possible weaknesses* in *that which is on offer*. The responses to the K&B questionnaire have taken their place in the public record, alongside all other relevant published material.⁶ If the burden of proof with regard to a presumption of liberty lies with the interventionists, however, the burden of proof with regard to a presumption for the status quo lies with the liberalizers. And the difficulty in proving a negative is often remarked. In my adopted position I am aiming to persuade the reader of a negative—that no case worthy of overcoming the presumption for liberty exists—with regard to a status-quo intervention. Such a position calls for a certain aggression. Indeed I have found that when trying to locate the possible weaknesses of an argument, the dominant initial strategy is to assume that the argument is wrong. But I do not beg the question: there is no conclusion herein that the argument for pre-market approval *is* wrong. My aggressive engagement with each respondent’s case for pre-market approval could turn up possible weaknesses, yet on reflection those weakness might seem unimportant or otherwise not fatal to the case. And so, the dissertation proceeds to a summation that provides such reflection upon the survey responses, and only then to the succeeding section on the published argumentation for pre-market approval.

⁶ The responses to the K&B questionnaire have been analyzed elsewhere, e.g., by Flanigan (2012, 287ff.).

The 14 respondents whose answers I engage in the next section (again, these are the all of the respondents who support pre-market approval, say there is a market-failure rationale, and who offered substantial responses to the open-ended questions), listed here in the order that I engage them, are: Kenneth Arrow, Pedro Pita Barros, Cornelis Boersma, Don Husereau, Randall P. Ellis, Marc L. Berger, John E. Brazier, Anthony John Culyer, F. M. Scherer, John Hutton, C. Daniel Mullins, Nikos Maniadakis, Karl A. Matuszewski, and Gérard de Pouvourville. The deviation from alphabetical order is done only to ease my presentation; where I found myself wanting to refer to something I had written in reaction to another respondent, I simply moved that respondent to an earlier position in the section.

Here is a summary of these 14 respondents' answers to key closed-end questions in the K&B questionnaire:

Q5b. Which of the following describes the nature or source of the market failure that justifies the policy requiring pre-market approval? Please be sure to check any and all that you believe to apply.

Those who checked "Imperfect information": Arrow, Barros, Boersma, Husereau, Ellis, Berger, Brazier, Culyer, Scherer, Hutton, Mullins, Maniadakis, Matuszewski, de Pouvourville (all 14)

Those who checked "Public-goods aspects of knowledge": Arrow, Barros, Boersma, Brazier, Scherer, Hutton, Maniadakis, Matuszewski

Those who checked “Government has superior ability to assure safety and efficacy”: Boersma, Husereau, Maniadakis, Matuszewski

Those who checked “Other”: Arrow, Boersma, Ellis, Brazier, Culyer, Scherer, Matuszewski, de Pouvourville

Q7b. Do you believe that consumers or patients systematically err when coping with uncertainties related to health and treatment?

Yes: Arrow, Barros, Boersma, Husereau, Ellis, Berger, Brazier, Scherer, Hutton, Mullins, Matuszewski

No: Culyer, Maniadakis, de Pouvourville

Q9b. Do you believe that doctors systematically err when selecting and prescribing therapies?

Yes: Barros, Boersma, Husereau, Ellis, Brazier, Hutton, Mullins, Matuszewski

No: Arrow, Berger, Culyer, Scherer, Maniadakis, de Pouvourville

Q11b. Say the policy that requires pre-market approval was eliminated and, in its place, a policy was implemented allowing new pharmaceuticals/devices and initially classifying them as requiring a doctor’s prescription (pending a review process to consider dropping the prescription requirement). Do you think such a liberalized system would be superior to the current system?

Yes: none

No: all 14

Q13b. Do you believe that uncertainty *per se* constitutes a market failure?

Yes: Barros, Berger, Maniadakis, de Pouvoirville

No: Arrow, Boersma, Husereau, Ellis, Brazier, Culyer, Scherer, Hutton, Mullins, Matuszewski

Q17b [Asked only if respondent did *not* check "Public-goods aspects of knowledge" in Q5b.]. You indicated that public-goods aspects of knowledge do not justify the policy requiring pre-market approval. Is that because you think such aspects are better addressed by subsidizing the generation of knowledge, e.g., via the National Institutes for Health?

Yes: Husereau, Berger, de Pouvoirville

No: Ellis, Culyer, Mullins

Q18b [Asked only if respondent *did* check "Public-goods aspects of knowledge" in Q5b.]. You indicated that public-goods aspects of knowledge are a source of the market failure that justifies the policy requiring pre-market approval. Do you think that this source of market failure would be better addressed with a policy that subsidizes the generation of knowledge, e.g., via the National Institutes for Health?

Yes: Boersma, Matuszewski

No: Arrow, Barros, Brazier, Scherer, Hutton, Maniadakis

Q20b. Imagine a new pharmaceutical being developed within the current regulatory system and brought all the way through to FDA approval. Do you think the policy that requires pre-market approval induces the generation of more knowledge about the new pharmaceutical than there would have been in the absence of the policy?

Yes: all 14

No: none

Q22b. As compared to the current system, would you favor making approval of a new drug automatic upon completion of the safety and efficacy testing processes specified by the FDA, regardless of what those testing results turned out to be?

Yes: none

No: all 14

Q24b. [Asked only if respondent checked "Government has superior ability to assure safety and efficacy" in Q5b.] You indicated that a superior ability of government to assure the safety and efficacy of pharmaceuticals justifies the policy requiring pre-market approval. Does that superiority stem from the FDA having special expertise in evaluating safety and efficacy?

Yes: Boersma, Maniadakis, Matuszewski

No: Husereau

Q26b. [Asked only if respondent checked "Government has superior ability to assure safety and efficacy" in Q5b.] Would you say that impartiality or commitment to the public good are sources of the government's superior ability to assure safety and efficacy?

Yes: Boersma, Husereau, Maniadakis, Matuszewski

No: none

Q29b. As compared to the current system, would you favor a reform so that pharmaceuticals approved by the FDA counterparts in Europe, Japan, Canada, or Australia were automatically approved for the United States?

Yes: Barros, Boersma, Brazier, de Pourville

No: Arrow, Husereau, Ellis, Berger, Culyer, Scherer, Hutton, Mullins, Maniadakis, Matuszewski

Q31. Prior to 1962, the FDA did not consider efficacy when making drug approval decisions. Doctors today are at liberty to prescribe drugs for "off-label" use—that is, for use where there has been no FDA evaluation of the drug's efficacy. However, as part of the current pre-market approval process, the FDA

requires proof of efficacy in the drug's "on-label" use(s). Would you favor dropping efficacy requirements from the pre-market approval process?

Yes: none

No: all 14

Q32. Efficacy requirements were introduced in 1962. Do you believe that the pre-1962 record shows systematic failure in assuring efficacy?

Yes: Arrow, Berger, Brazier, Culyer, Scherer, Mullins, Matuszewski, de
Pouvourville

No: Barros, Boersma, Husereau, Ellis, Hutton, Maniadakis

ENGAGEMENT WITH K&B SURVEY
RESPONSES SUPPORTING PRE-MARKET APPROVAL

Kenneth Arrow

Stanford University, Professor of Economics and of Management Science and
Engineering Emeritus⁷

summoned as a selected luminary in the fields of information or health economics⁸

Kenneth Arrow strongly supports pre-market approval, and he invokes several market-failure rationales. The first is imperfect information.⁹ The first probe into that rubric concerns systematic erring by patients, and Arrow says he believes in such erring. When asked in what way such erring is manifested, he explains:

Information is difficult to acquire and understand. The average consumer is in no position to find the information for him- or herself

⁷ Affiliations and titles given in this document are in each economist's own words, from their response to K&B question C. I added necessary information to one economist's affiliation; that single addition is enclosed in brackets.

⁸ The six groups comprising K&B's initial sample are described and listed in Klein and Briggeman (2010, 102-105). In this paper I provide additional detail (e.g., the specific journal with which an economist was associated).

⁹ "Imperfect information" and "public-goods aspects of knowledge" are terms used in the questionnaire itself to identify two broad classes of ideas about market failure. The recurrence of these terms throughout this analysis should be understood in that sense.

and will therefor[e] be likely [to] err relative to the full information available.

So the average consumer is likely to err relative to the full information available.

Economists normally would reject the idea that acting with less than full information, by itself, constitutes *systematic* erring. Systematic erring means erring in a predictable or regular direction away from the right choice, like a steering mechanism that systematically pulls to the right. Arrow has not provided any description of how consumers might systematically miss the bull's-eye; he simply says they are unlikely to hit the bull's-eye. Such is the point of the subsequent question in the K&B questionnaire that asks whether the respondent believes that uncertainty *per se* constitutes a market failure—yet Arrow says there that uncertainty *per se* is not a market failure. So I believe the question remains effectively unanswered: what or where is the systematic erring by patients?

When asked whether doctors systematically err, Arrow replied No, so no followup question was asked. I presume that it is not safe to infer that he thinks doctors *do* take advantage of “the full information available,” but that underscores the absence of a satisfactory answer regarding patients.

When asked whether there is any other sense in which imperfect information is a source of market failure justifying pre-market approval, Arrow made the short reply:

“Avoidable imperfect information may inhibit the entry of rivals.” I interpret this to mean the following: When Firm A develops a new drug, it has more information about that drug than does its potential rival Firm B and other firms, and that Firm B or some other rival is less likely to enter that market than it would if it had all the information that Firm A had about the drug. The premises might have some validity, but for this argument to be incorporated into a justification of pre-market approval, Arrow would have to maintain that by virtue of pre-market approval Firm A makes known more information about the drug than would be the case without pre-market approval. The thrust of the argument would be that the pre-market approval process induces a sharing of knowledge.

Indeed, this construction of Arrow’s reasoning would seem to be confirmed by his responses to the question: “*Say the policy that requires pre-market approval was eliminated and, in its place, a policy was implemented allowing new pharmaceuticals/devices and initially classifying them as requiring a doctor’s prescription (pending a review process to consider dropping the prescription requirement). Do you think such a liberalized system would be superior to the current system?*” To this Arrow responds No and explains:

There would be no publicly available evidence on the efficacy and safety of the drugs, except what is supplied by interested parties.

Such a justification leads to the challenge posed by the questionnaire in question 22b: “As compared to the current system, would you favor making approval of a new drug automatic upon completion of the safety and efficacy testing processes specified by the FDA, regardless of what those testing results turned out to be?” To that question, Arrow gives a qualified No, adding:

This is a closer call than the abolition of the approval process. Nevertheless, the dissemination of the relevant information is too costly for the patients (and the doctors) to permit the sale of drugs that have not met the appropriate standards. (There are many parallels in other fields.)

Assessing the whole of Arrow’s responses regarding imperfect information, then, I interpret him as having put forward two market-failure rationales and two corresponding remedies:

I. “Avoidable imperfect information may inhibit the entry of rivals.” Pre-market approval remedies this failure via the supply of “publicly available evidence on the safety and efficacy of the drugs” by a disinterested party.

II. “[T]he dissemination of the relevant information” to the patients—who would find the information “difficult to...understand,” even if they had it—and to the doctors is costly. Pre-market approval remedies this failure by not permitting “the sale of drugs that have not met the appropriate standards.”

Re: I. Rationale I and its corresponding remedy do not go to the heart of pre-market approval policy, which is a prohibition on the marketing of drugs the FDA deems to be unsafe or ineffective. As suggested by question 22b, it should be quite possible for the U.S. government to lift that prohibition while continuing its efforts toward the provision of “publicly available evidence on the safety and efficacy of the drugs.” Nevertheless, I am inclined here to explore this rationale and remedy in some depth, as it makes usefully bold claims about important information-related matters.

I decompose Arrow’s statement that, after the elimination of pre-market approval, “There would be no publicly available evidence on the efficacy and safety of the drugs, except what is supplied by interested parties,” into two possible concerns:

IA. What publicly available evidence exists will be supplied by interested parties.

IB. Interested parties will not generate enough publicly available evidence.

I will make a brief demonstration that these two concerns, as stated, are not definitively resolved under the status-quo regime, and therefore that a more elaborate argument than Arrow provides would be necessary to demonstrate the relative undesirability of a liberalized regime.

Re: IA. Today, the relevant studies of a drug’s safety and efficacy are typically undertaken (or, at least, paid for) by an interested party, i.e., the drug’s sponsor. Therefore, Arrow’s implication that the current policy regime does yield “publicly available evidence...supplied by [a disinterested party]” could only have meaning if his supplier of evidence is understood to be not the primary investigator (the sponsor or its research vendor) but rather some entity or network that certifies the investigators, their methods, and their results.

The FDA is of course today not the only entity or network that validates or certifies evidence on drugs. But even if one were to treat analytically the status quo as if it were reducible to a single ‘central’ certification network or process led by the FDA, one would have to conclude that this network or process is itself not monolithically disinterested. Daniel Carpenter (2010, 566-571) argues that “most of the work” of approving research protocols, monitoring studies, and assuring data quality is done by institutional review boards (IRBs), which he describes as the FDA’s “satellite regulators.” An IRB is generally tied closely to the researchers overseen by the IRB, and very often is part of the same organization (e.g., the university or hospital) that employs those researchers. Carpenter describes how the FDA exerts influence over the IRBs:

[T]he Administration has created a series of veto points—more than five thousand of them, according to one recent estimate—over clinical research while still retaining its own ability to place a clinical hold upon

the research, to reject the IND application for a later phase, or to reject the eventual new drug application. [...] Because each board is monitored by the Administration and can be potentially disqualified by the agency, strong reputation-based incentives exist to toe the line on FDA rulemaking. Because IRB disqualification is tantamount to disqualification of an entire research institution—firms will avoid universities and contract research units whose IRBs have been disqualified, and these organizations will face difficulty in procuring grants—review boards and the universities they serve have incentives to remain thoroughly and fearfully accountable to the Administration. (Carpenter 2010, 567-568)

Carpenter later examines the FDA's monitoring of IRBs:

Just how intensive or exhaustive has Administration oversight been? Data are insufficient to permit a good answer to this question, but some patterns from the past two decades can be gleaned from FDA and congressional reports. From fiscal year 1986 to fiscal year 1995, for instance, the FDA's Center for Drug Evaluation and Research conducted 1,712 inspections of establishments for compliance with FDA informed consent requirements. From 1991 to 1995, the FDA issued an average of 158 IRB inspection reports per year. [...]

From January 1993 to November 1995, the FDA found violations serious enough to merit a warning letter in thirty-one cases. The agency has never disqualified an IRB, but in response to FDA findings of serious noncompliance with federal regulations, research institutions have disbanded their IRB more than sixty times in the past two decades. (ibid., 570)

If there are over 5,000 IRBs and 1,700 inspections are conducted in a decade, the rough calculation suggests that an IRB could expect to be inspected one time in a generation. Further, note that the “strong reputation-based incentives” that Carpenter says assure an IRB’s accountability to the FDA are future grants and contracts that the IRB’s parent organization—which, again, is often the same organization that employs the researchers the IRB is supposed to oversee—will stand to lose if the IRB is disqualified. In their writings criticizing for-profit IRBs, Trudo Lemmens and Carl Elliott have emphasized both the looseness of FDA oversight of IRBs and the similarity of the incentives facing IRBs and the researchers they oversee:

It is widely recognized that the commercialization of medical research creates serious conflicts of interest. What is often overlooked is that IRB review, which is often expected to provide protection against such conflicts, has also become commercialized. Some industry-funded trials

are reviewed by in-house IRBs set up and funded by pharmaceutical companies or CROs [contract research organizations] themselves; others are reviewed by commercial, for-profit IRBs. ...

The countries that have allowed these private IRBs to flourish have also failed to regulate them carefully. Neither the US nor Canada has placed any serious restrictions on the establishment of new IRBs. Although an IRB registry has recently been set up for federally funded research in the US, and although the FDA and Health Canada sporadically inspect IRBs involved in the review of clinical trials, they do not have formal registration and approval processes for IRBs. (Lemmens and Elliott, in Emanuel et al. 2006, 942)

Meanwhile, Arrow says a source of pharmaceutical market failure is that drug manufacturers—who can expect to lose goodwill and face litigation in the wake of negative publicity about one of their products—“do not have the right incentives to assure efficacy and safety.” If Arrow were to think and speak about IRBs, would he hold that they, too, do not have “the right incentives”?

Under this analytically reduced status-quo regime of FDA pre-market approval, then, ‘interested’ (i.e., not disinterested) investigators generate evidence that is certified by a loose network of observers, the most immediate of which is often another unit within the investigator’s own organization. The FDA is involved indirectly, by infrequent

oversight of the immediate observers, and also directly, by its evaluation of standardized applications to begin research (the Investigational New Drug form, or IND) and to sell product (the New Drug Application, or NDA).

A trained economist can readily identify potential conflicts of interest, agency problems, and weak incentives within the status-quo regime described above, and so—even if one were to make the extreme and doubtful assumption that the internal operations of the FDA are carried out in a remarkably disinterested fashion¹⁰—to think that the overall state of affairs is equivalent to the production of evidence by one disinterested party is too pat. Under a reformed regime—or under a continuance of the status quo—research would be conducted by parties of varying ‘interestedness’, and one or multiple certifiers of that research conceivably could approach or surpass the FDA in ‘disinterestedness’ (and still in any event the consumer would be required to place his or her trust in something that is imperfect).¹¹ Research under the current regime therefore cannot be judged *prima facie* to have been generated by a process less ‘interested’ than

¹⁰ Fleischhacker and Cohen (2009, 29) say there are “daily revelations of [the FDA’s] politically motivated decisions, cozy relationships with industry, and conflicts of interest.” Jefferson et al. (2011) write that “Governments currently have this responsibility [to provide unbiased systematic assessments of drugs], but regulators are under-resourced and powerful disincentives for rigorous review exist because candid analyses may undermine current policy.”

¹¹ Arrow complained that information is produced by “interested parties.” I am tempted to infer from this a claim that the FDA is *perfectly* disinterested, but I refrain as Arrow did not say “perfectly.” Had I made that inference, Arrow could object and characterize his claim as being that the FDA only needs to be, and is, *the most disinterested* party. But from there, would we not be drawn right into the questions that I proceed to raise about relative ‘interestedness’ and the desirability of a monopoly certifier?

that of some liberalized regime. But Arrow does not provide evidence with regard to the disinterestedness of the status-quo regime or its possible alternatives. Perhaps there is little evidence to be had. But in the absence of evidence we effectively have rival presumptions, that for the status quo and that for liberty. The economists' discourse about market failure is based upon the Smithian presumption for liberty.

If we drop the particular analytical reduction of the processes generating pharmaceutical information that is offered above—that reduction being: research by 'interested' parties is certified by less interested entities—we may consider plausible mechanisms by which pre-market approval could lead to an *increase* in the influence of interested parties. David Healy (2012) has argued that pre-market approval, in conjunction with prescription requirements, has caused a suite of questionable outcomes related to pharmaceutical marketing. When a small group—physicians, in the context of prescription requirements—is in control of the entire market demand, it becomes economical for pharmaceutical companies to aggressively seek influence over that small group (Healy 2012, 44-49). Healy believes that pharmaceutical companies have by now achieved so much conceptual power within medicine that they prefer new drugs to have prescription-only status (*ibid.*, 51-52). Under Healy's interpretation, at several levels of discourse and practice the status quo is beset with an enormous amount of information produced by highly interested parties, both about drugs and about health problems the drugs purport to address. Healy calls for several reforms:

Senator Kefauver adjusted the rules one way, perhaps the right way for his time, but in a manner that seems to be contributing to our problems now. Are there any adjustments that might steer medicine back toward what it could be and at the same time give us a glimpse of what a properly human economy (*oikumene*) might look like? There may be other steps to take, but following Kefauver we can look at company practices of sequestering clinical trial data that inhibit the ability of doctors to practice data-based medicine, the availability of medicines by prescription only, and the current patenting arrangements for drugs.

Reforms in these areas will require wisdom—having good intentions is not sufficient. Social arrangements have a great capacity to deliver exactly the opposite outcomes to those their proponents intended, as perhaps Kefauver’s 1962 Act demonstrates better than anything else. (Healy 2012, 239)

At a minimum, I believe Healy’s narrative is valuable in demonstrating how insufficient it is, when aiming to show that pre-market approval leads to the dissemination of information that is less biased, merely to assert that such is the necessary result of a pre-market approval regime. So there are miles to go from the point of Arrow’s response.

Re: IB. In the absence of the pre-market approval policy, conventional economic logic suggests that the marketing of a new drug will involve the production and release of

whatever information on efficacy and safety is expected to increase seller profits. Such information will obviously be biased, but exactly that obviousness should prompt companies to seek certification of that information by a less interested party, at least to the extent it aids profitability. A certifier itself may require public disclosure of the information upon which its certification was based. And aside from that information produced at the behest of suppliers, as a drug passes out of supplier hands and into circulation, some information will surely be produced by others following their own peculiar incentives, others such as healthcare organizations, activist groups, scholars, journalists, and so on.

Pre-market approval transforms the situation by fixing sales at zero for some period (prior to an approval at least, and possibly forever after a rejection). A naïve guess is that, by prohibiting all but FDA licensees from studying or distributing a given drug, publicly available information about the drug is reduced by pre-market approval. However, the promises of patent protection and marketing exclusivity (Junod 2004) are strong incentives for firms to seek licenses, explore new drugs, and submit to FDA direction in the conduct of study. The public fate of information generated by these processes is more or less determined by the FDA's approval decision: some information is made public regarding approved drugs, and very little is made public about unapproved drugs. In the wake of a decision to approve a drug, the FDA typically publishes several reports to justify its decision, including some detail about the studies of safety and

efficacy conducted under its purview.¹² But disclosure of information about approved drugs does not extend as far as a layman might presume: “the pharmaceutical industry has long taken the position that the data from clinical trials of drugs constitute proprietary trade secret information.... The FDA has consistently supported this position and withheld the data from public disclosure as a matter of administrative practice, although the statutory language invoked in support of this position is ambiguous” (Eisenberg 2005, 736). And by contrast, for unapproved drugs FDA generally will not disclose even the fact that a sponsor has applied for permission to investigate or market the drug, let alone any information on safety or efficacy (FDA Transparency Task Force (hereafter “FDA TTF”) 2010, 32, 36).

So it may be plausible to claim (though perhaps with low confidence), as Arrow does in his response to question 20b, that pre-market approval may induce the generation of more knowledge about a newly approved drug than there would be in the absence of the policy. Viewed as an isolated effect, that could be a plus for the law-abiding “average consumer” who needs not know about the safety and efficacy of drugs that he doesn’t have the option of taking.¹³ But here we are considering Arrow’s argument that pre-market approval is justified because imperfect information inhibits entry—and

¹² See the FDA’s “Drug Approvals and Databases” website.

¹³ By “isolated effect” I mean solely the benefit from increased generation of knowledge, which is importantly distinct from whatever effects pre-market approval has on the *use* of knowledge by physicians and patients. It could be, for instance, that pre-market approval induces physicians and patients to rely heavily on the judgments of the compulsory certifier, but that the compulsory certifier does not exercise good judgment regarding the (increased) amount of knowledge at its disposal.

information about *unapproved* drugs is very valuable to pharmaceutical researchers (FDA TTF 2010, 39-41; McGarity and Shapiro 1980, 847-848). One imagines that researchers often waste resources by traversing intellectual alleys that, unbeknownst to them, some competing ‘first’ researchers have already concluded will not lead to the production of an FDA-approvable molecule. But in the hypothetical liberal world where the ‘first’ researchers may proceed to market on their own convictions, some profit-directed public disclosure of their research would occur, and more information would be generated by others once the drug circulated beyond the supplier. For Arrow’s “avoidable imperfect information” rationale for pre-market approval to become compelling, he would need to explain how the non-divulgence and loss of such information would be offset by greater gains elsewhere.

But, again, Arrow’s concerns about insufficient “publicly available evidence” (IA. and IB.) cannot by themselves lead us to the conclusion that pre-market approval should be preferred to other means of remediation. An alternative remedy, one that aims at directly undoing the market failure, would be for the government to produce the evidence itself and publish that evidence. Another alternative remedy could be reforms to intellectual property law, through which large informational disparities and inhibition of entry are, after all, deliberately created. If government provision of evidence or IP reform can address Arrow’s concern directly, there hardly seems a need to address the concern indirectly, e.g., through the informational effects of a ban on products the FDA deems unsafe or ineffective. So this leads us to Arrow’s second set of concerns (II.).

Re: II. Arrow's assertion that "dissemination of...information is too costly" I find difficult to interpret in the Internet era. He can't believe the limiting factor is data transmission costs, for those are effectively zero. I also see nothing in Arrow's responses to indicate belief that patients or doctors lack the proper incentives to seek out "the relevant information." He did express the concern about whether there will be "publicly available evidence on the safety and efficacy of the drugs," but he seemed to consider this matter to be satisfactorily addressed by the reform, proposed in question 22b, that would leave FDA testing processes in place but make approval automatic.

What is left are Arrow's concerns that "Information is difficult to...understand," and that "The average consumer is in no position to find the information for him- or herself." It is possible to imagine policy regimes that are at least somewhat liberalized from the status quo but that purport to address these concerns, as shown in Table 1. Under Table 1's Variant #1, information on a drug would be almost exactly as difficult or easy for an "average consumer" to understand as it is today: reams of information on each drug would exist, alongside an FDA judgment on safety and efficacy (viz., an FDA approval decision or certification) that can be represented in more or less one 'bit' of information. Under Variant #2, the 'bit' of information conveying the FDA judgment would be delivered directly to most consumers at the time they acquire the drug in question. Would Arrow support Variant #2, given that it addresses his concerns that

“Information is difficult to...understand,” and that “The average consumer is in no position to find the information for him- or herself”?

Table 1. Four policy regimes

	Reform Proposed in Question 22b (rejected by Arrow)	Variant #1 on Question 22b	Variant #2 on Question 22b	Status Quo
Mandate safety and efficacy testing specified by FDA	Yes	Yes	Yes	Yes
FDA forms a judgment on safety and efficacy	Unspecified	Yes	Yes	Yes
Mandate that products be labeled with FDA judgment	Unspecified	No	Yes	No
Ban products FDA deems unsafe or inefficacious	No	No	No	Yes

I sense that Variant #2 would in fact not satisfy Arrow. Arrow was asked in question 5b “*Which of the following describes the nature or source of the market failure that justifies the policy requiring pre-market approval? Please be sure to check any and all that you believe to apply.*” Of the four responses, Arrow selected three—“Imperfect information,” “Public-goods aspects of knowledge,” and “Other”—and the lone response he did not select was “Government has superior ability to assure safety and efficacy.” So

on the one hand, he does not seem to think the FDA has special expertise. Yet he does not offer the idea of a reform such as Variant #2, viz., certification without banning of uncertified products, even though such a reform is an obvious possibility.¹⁴ And unlike some respondents, Arrow in his own words directly faces up to the reality that pre-market approval constitutes a ban on the sale of unapproved drugs (both in his responses to questions 23b and 34). So I feel confident in my prediction that Arrow would reject Variant #2—but it is hard to say exactly why.

Perhaps Arrow would say that among those things “the average consumer” would fail to understand is that extraordinary attention and extraordinary respect should be accorded to the FDA judgment, and therefore that merely informing the consumer of the FDA judgment is insufficient. Such an interpretation of Arrow’s responses is somewhat speculative, and it may run somewhat counter to Arrow’s failure to select “Government has superior ability to assure safety and efficacy” as a source of market failure, but it seems necessary to make sense of Arrow’s presumed opposition to Variant #2. Arrow does not, of course, put forward an argument explaining why consumers may not accord

¹⁴ Arrow (1963, 967) raises the possibility of certification as an alternative to licensing of physicians: “The state or other agency can certify or label, without compulsory exclusion. The category of Certified Psychologist is now under active discussion; canned goods are graded. Certification can be done by nongovernmental agencies, as in the medical-board examinations for specialists.” He then writes: “The certification proposal never seems to have been discussed seriously. It is beyond the scope of this paper to discuss [such] proposals in detail. I wish simply to point out that they should be judged in terms of the ability to relieve the uncertainty of the patient in regard to the quality of the commodity he is purchasing, and that entry restrictions are the consequences of an apparent inability to devise a system in which the risks of gaps in medical knowledge and skill are borne primarily by the patient, not the physician.”

sufficient respect to the FDA judgment; however, other respondents to the K&B survey, in particular Don Husereau, do offer such arguments, and I address them where they are put forward.

* * * * *

Besides imperfect information, Arrow also selected the rubric of public-goods aspects of knowledge as giving rise to market failures that justify pre-market approval. Within that rubric he was asked: *“You indicated that public-goods aspects of knowledge are a source of the market failure that justifies the policy requiring pre-market approval. Do you think that this source of market failure would be better addressed with a policy that subsidizes the generation of knowledge, e.g., via the National Institutes for Health?”* His answer was No, and he explains:

Additional information through the NIH or (preferably) a dedicated information-disseminating information (like NICE in the U.K.) would be valuable, particularly in acquiring and diffusing information derived from post-approval use. It would not be a substitute for the controlled tests which are used in the approval process.

It seems reasonable to propose that any funding by the government would carry the stipulation that the results be made publicly available. So it would seem that the NIH

approach could go far in addressing both Arrow's express knowledge-sharing concern and his public-goods rationale—the government pays for research and sees it published. Yet he entirely neglects to explain why it is not a better approach. I feel that he begs the question when saying “It would not be a substitute for the controlled tests which are used in the approval process.”

To question 29b, “*As compared to the current system, would you favor a reform so that pharmaceuticals approved by the FDA counterparts in Europe, Japan, Canada, or Australia were automatically approved for the United States?*”, Arrow gives a qualified No, explaining:

My correct answer, not provided for in your choices, is, I cannot be sure. It will certainly depend on the degree of coordination among the different countries. An international approval body makes sense; an unrestricted reliance on the agencies of other countries would require at least a study of the quality of their performance.

Arrow says that going along with the proposal would “require at least a study of the quality of their performance.” This is the only time in his responses that Arrow refers to the prospect of studying a questionnaire-proposed reform to see if it makes sense. The salient difference would seem to be that this reform is a proposal to rely on different regulators, as opposed to the other reforms that proposed reliance on voluntary or

spontaneous mechanisms. Here Arrow expresses great concern about the absence of such a study. Perhaps the reform at hand is ‘close enough’ to status quo arrangements to merit study, whereas the others are distant enough to be dismissed without concern for evidence. But consistent with his other responses Arrow seems to place the burden of proof on those who would reform the status quo, as opposed to on those who support status-quo interventions.

* * * * *

Arrow also selected the “Other” market-failure option, and offered the brief explanation: “The firms do not have the right incentives to assure efficacy and safety.” This is a comment I shy away from interpreting. I could only guess at how Arrow would define the “right incentives,” and why firms’ not having those incentives constitutes a market-failure rationale for pre-market approval. Incentives facing other parties are also relevant to the question of market failure; for example, short-selling investors have strong incentives to research drug safety concerns (Gale 2009, 1979-1980). How “right” are those incentives? And what about the incentives that face the regulators?

Carpenter has argued that FDA employees, in their actions taken as FDA employees, primarily seek to enhance the reputation of the FDA:

Consider first the individually based motivations of government regulators. Organizations and their members in numerous walks of life aim less for profit itself, less for power itself, and more for reputation and the associated benefits that it brings: prestige, status, and authority. In many respects, as psychologists and organizational scholars have emphasized, the pursuit of these ends is not entirely conscious but instead is built into the very cognitive and emotional fabric of the organizational human. For the individual populating regulatory agencies, this logic implies that pay, budget maximization, and other material goods will be valued less highly than status and esteem. [...]

Consider next the imperatives of organizational management. If an agency's reputation partially or wholly underlies its authority and power, its more authoritative and committed members may act to preserve, maintain, and enhance the reputation. (Carpenter 2010, 55-56)

It may indeed have proven analytically fruitful for Carpenter to assume that institutional pressures push individual regulators primarily to seek enhancement to the Administration's reputation.¹⁵ But it might prove similarly fruitful to assume that actions

¹⁵ I emphasize institutional pressures upon individual regulators, as opposed to propensities intrinsic to the individual regulators as persons, as it is doubtful that government employees are very differently motivated from other persons. "Public servants were 6.5 percentage points more likely than private-sector employees to report that they worked so hard that it sometimes interfered with their lives, but having more interesting work, better opportunities to help others, and higher average age almost

taken by employees of a private firm on behalf of that firm stem from their concern for the firm's reputation. We might then show that the things the employees do are roughly as well explained by the reputation-seeking assumption as by a profit-seeking assumption. But this would be to miss the point. We assume that institutional pressures within the firm guide employees to find profit-enhancing actions because the firm is likely to go out of business if *and because* it fails to profit. If somehow a firm profited despite a terrible reputation, the firm likely would continue to exist; if it made losses despite a sterling reputation, it likely would fail. Similarly, an agency of the government will 'go out of business' if and because Congress eliminates funding for the agency. We can imagine that Congress might eliminate an agency even if the agency's reputation is sterling.

It might be argued that, since some of the possible reasons for which Congress might eliminate an agency are political factors beyond the control of anyone at the agency, we should assume the agency primarily seeks merely to enhance its reputation with Congress, this being 'all it can really do' to survive over the long run.¹⁶ However, the same could be said of a firm, that economic factors well beyond its managers' control might cause the firm to become unprofitable. Does that mean there is great analytical hay

entirely accounted for that difference. [...] In both sectors, an interesting job that allows one to help others and a strong desire for job security appeared to increase the probability that one will put in extra effort, and the size of the effect appeared to be about the same in both sectors." (Frank and Lewis 2004, 46)

¹⁶ Over the short run, to survive—or, at least, to continue to function—an agency must take care not to exhaust its current allocation too soon. This is roughly tantamount to maintaining 'profitability' over the budgetary period.

to be made of the notion that the managers of a firm do not ‘really’ direct their long-term planning at the generation of profits, but instead that they simply aim at the ‘doable’ task of enhancing the firm’s reputation with consumers? If by focusing on that notion we would ignore the power and motivations of the firm’s *owners*, then certainly not. Economists are on fine ground in thinking of employee concern for reputation as falling out of institutional pressures conducing to organizational survival and prosperity, pressures that must be generated within any surviving organization, private or public.

Thus it seems to me (and, it should be said, to Carpenter¹⁷) that FDA employees’ attention to the agency’s reputation with Congress, however assiduous it may be, does not resolve the question of whether any particular governmental policy is wise or even well executed. For what motivates Congress, or the President, or the voters, in their roles

¹⁷ Both toward the beginning and at the end of his lengthy *Reputation and Power*, which is devoted to showing how FDA’s maintenance of its reputation has enabled its accumulation of power, Carpenter emphasizes that the book does not substantially engage the question of whether the FDA is desirable:

“Government regulators bear formal authority to confer or revoke legal rights of production, market distribution, and advertising. Government regulators can change the economic, social, scientific, and political agenda—the set of products developed, the set of issues raised in national debate, the measurements used to develop, produce, and market new products. Government regulators shape the concepts of science and economy. Whether these effects are to be praised or lamented is a topic for a separate debate. A normative discussion of whether regulatory power is insidious or desirable (or some combination of the two) should be premised upon an awareness of what powers are operating” (Carpenter 2010, 63).

“Should a government agency, in a democratic republic—one governed by a constitution and the rule of law—have these powers? A more compelling answer to this question demands a separate, still empirical but more philosophical inquiry” (Carpenter 2010, 751).

as quasi-owners of the FDA? How attentive or knowledgeable are they? How good is their judgment? Such questions are matters of endless controversy among scholars of political economy.¹⁸ And so it is robustly unclear, on the face of things, whether the FDA has “the right incentives to assure efficacy and safety” while “firms” do not. I am more prepared to make the lesser claim, with Carpenter, that the FDA has strong incentives to maintain its reputation with Congress. Is it any more controversial to say that doctors and pharmaceutical firms have strong incentives not to poison their customers and to serve them well if possible? Congressmen would like efficacy and safety to prevail, as would voters, as would doctors, firms, and consumers. In the absence of some extensive analysis, the sets of incentives facing these groups are not readily classifiable as right or wrong, weak or strong, sufficient or insufficient. But we do not know what analysis underlies Arrow’s assertion, as he did not provide a citation.

* * * * *

In the final question soliciting general comments, Arrow replied:

There is a broad principle of economies of scale in the collection of information which is applicable, for example, to national income data. I cannot imagine a substitute in the case of testing drugs for both safety and efficacy. The only possible controversy is whether the government

¹⁸ See, e.g., Wittman (1995) and Caplan (2007).

or the patient or the physician should make the final decision on the use of the information.

Economies of scale exist when an organization has declining average costs in the production of some good, and such a situation is often related to the notion of a natural monopoly. Arrow asserts that such economies exist “in the case of testing drugs for both safety and efficacy.” Under the status quo, the producing firms themselves see through the expensive clinical trials that are the main input into pre-market approval decisions: A firm funds trials and collects the information about its own drug for presentation to the FDA. It is not obvious, with regard to information about testing of a single new drug, that economies of scale exist beyond the size of the producing firm. Arrow speaks of the “collection of information.” Certainly it is valuable to have a compendium of the testing information for many drugs, but compendia of drug information have long and often been produced at private initiative (e.g., General Medical Convention 1820; Wood and Bache 1833; Martindale and Westcott 1883; see on this Wood 1931; Kremers and Urdang 1976, ch. 15; Whittet 1983). The historical record gives little reason to think there is a natural monopoly in these matters. Furthermore, even in the highly doubtful event that there were such a natural monopoly, what is the supposed harm—that a natural monopolist producing a compendium of drug information will undersupply the market for drug information? Doesn’t the existence of libraries, as well as professional norms in the medical field, go a very long way toward resolving that concern? And might not physicians use their investment in the costly drug compendium as a worthwhile signal of

their quality? In lieu of evidence regarding these matters Arrow provides the report that he “cannot imagine a substitute.”

Arrow’s reference to “national income data” as an example of “a broad principle of economies of scale in the collection of information” deserves attention. National income and product data, e.g., the GDP figure for the United States, is one of many aids to macroeconomic policymaking, and it is of but limited utility to anyone not involved in setting those policies. The U.S. government is able to estimate its GDP figures relatively easily once it has in hand the information generated during its sweeping census and tax collection activities, and, given its own need for macroeconomic indicators, it effectively judges that calculating the estimate is worth the small extra effort expended. But it is nigh impossible to imagine that the demand for national income data alone would justify all the coerced activity, i.e., tax compliance efforts, that yields up so much of the information now used to construct the GDP figure.¹⁹ The demand for national income data might well be satisfied by the use of less coercive sampling methods—along with whatever relevant information is otherwise publicly available—to produce an estimate that is just as reasonable.²⁰ Such a survey could be carried out by an agency of unremarkable size.

¹⁹ Cf. Piketty (2014): “To me, one of the main purposes of the wealth tax is that it should produce more information on wealth.”

²⁰ Survey methods already play a large role in the estimation of GDP, which in general cannot be measured with great precision (Landefeld, Seskin, and Fraumeni 2008). The surveys, including the quinquennial Economic Census, are generally compulsory. But if the goal is to produce a rough measure of national product, a compulsory survey of

Perhaps, one could creatively construe Arrow as addressing this answer to the study of drugs in use by the public, which in the context of pre-market approval can be part of what the FDA sometimes terms “post-marketing surveillance.”²¹ Here sampling may not work very well, e.g., in dealing with rare events. Widespread consistent reporting on patient experiences and collection of those reports by a central agency, such as the FDA attempts to promote with the FDA Adverse Event Reporting System (FAERS), might be desirable. But here we would be arguing that the study of drugs *as they are being used by the public* is difficult in certain ways that government involvement might ameliorate. It is obvious how this sort of argument could be used to justify something like the FAERS. But left undrawn is the connection between this, or any of the other matters discussed above related to “economies of scale in the collection of information,” and the pre-market approval regime. When imagining what would directly undo that possible source of market failure, we immediately imagine *collection of information*. But pre-market approval goes far beyond collection of information, and even beyond compelled testing (or compelled reporting), to the banning of products the FDA has not approved on grounds related to the results of such tests.

“all but the smallest businesses” ([such as the Economic Census](#)) may not be needed. The Census Bureau’s Annual Survey of Manufactures, for instance, is used by the Bureau of Economic Analysis in constructing the “annual GDP updates and weights for GDP deflators” ([link](#)) and is also compulsory but surveys only “a sample of all establishments that received a form in the previous Economic Census—Manufacturing” ([link](#)).

²¹ See, e.g.,

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm090385.htm>.

Arrow's final sentence about "the only possible controversy is whether the government or the patient or the physician should make the final decision on the use of the information" underscores an evasiveness in some of his responses. That question—"whether the government or the patient or the physician should make the final decision"—is not a possible controversy to be raised as an afterthought; it is the most certain controversy, and it animates the entire issue. The K&B questionnaire had been asking not merely that the respondent identify market failures in pharmaceuticals, but specifically for the market failures that justify pre-market approval. Arrow comes down squarely in favor of that particular form of intervention, but it would be hard to claim that he provided or pointed to a rigorous defense of such.

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Barros supports pre-market approval, but not strongly. He cites imperfect information as one source of market failure. When asked if patients systematically err in

coping with health uncertainties, he says Yes: “Patients overestimate benefits and patients with insurance do not take into account the opportunity cost of their consumption.”

When an insured patient fills a covered prescription, what is the opportunity cost of so doing? Even when the patient’s out-of-pocket expense for a drug is zero, still the patient should be characterized as choosing to forego some alternate course of therapy. But what reason is there to think that, *because* some treatments are inexpensive or free, the doctor who writes the prescription, or the patient, will err in judging the *therapeutic* merit of competing treatments? Certainly, therapies inexpensive to the patient are more likely to be chosen, but that is true whether patients are insured or not. Regardless: The FDA routinely claims not to take drug costs into account when making approval decisions,²² so these matters are essentially irrelevant to pre-market approval policy.

I interpret “Patients overestimate benefits” to mean that patients overestimate the value of medical products. Barros does not provide or point to any evidence in support of this claim. It may be somewhat obvious that, even if it were proven that the flat claim “patients overestimate benefits” is consistently true, this would hardly constitute a case for pre-market approval, but to make matters clearer I will briefly explore the role of expectations in a flat model (mirroring the claim).

²² For one example of this claim, see the FDA’s denial that costs were weighed in a decision related to the drug Avastin (FDA.gov 2010a, Q8). A recent exception occurred with regard to the drug 17P and is documented by Harris (2012).

Let E represent a patient's estimate of a product's value to the patient, R represent the value the patient would place on the product if the patient knew the product's real effects on her, and C represent costs that the patient incurs in the choice to use the product. If the patient is limited to two choices—use the product or don't—and the cost of not using the product is zero, the patient will use the product when $E > C$. Assuming no exact equalities among these values, there are six possible orderings of the values E , R , and C :

$E > R > C$, $E > C > R$, and $R > E > C$ (patient would consume the product);

$C > E > R$, $R > C > E$, and $C > R > E$ (patient would *not* consume the product).

Assume that a government has the power to intervene in the market for this product. Let I represent the change in the patient's costs of consumption that are brought about by intervention. The patient now chooses to consume the product when $E > C + I$. The patient's welfare when she consumes the product is given by $R_A - (C + I)$, and the patient's welfare when she does not consume the product is R_0 , where $R = R_A - R_0$.

Here is a matrix of possible outcomes:

Table 2. Effect of intervention on patient's welfare

	Effect of intervention on patient's welfare...	
	...if $E > C + I$ (Patient uses product)	...if $E < C + I$ (Patient does not use product)
$E > C$	$-I$	$C - R$
$C > E$	$R - C - I$	0

By limiting our examination to restrictive interventions (that is, to where $I > 0$), we can characterize the directional impact on welfare. Shaded cells indicate a negative impact, and boldface indicates a positive impact:

Table 3. Effect of restrictive intervention on patient's welfare

	Effect of restrictive intervention ($I > 0$) on patient's welfare...	
	...if $E > C + I$ (Patient uses product)	...if $E < C + I$ (Patient does not use product)
$E > R > C$	-I	C-R
$E > C > R$	-I	C-R
$R > E > C$	-I	C-R
$C > E$	0	

The presumption for liberty leads one to hesitate here with regard to what constitutes a case for intervention, since there are unfortunate knowledge effects, etc., that result from restrictions but are not captured in this model. Table 3 suggests, however, that restrictions are most likely to do good *not* whenever R is lower than E , but rather only when R is below E *and* below C . The model is a gross simplification, to be sure, but it suggests that when $C = 0$ (“patients with insurance do not take into account the opportunity cost of their consumption”), the potential case for intervention can be made not wherever $E > R$ (“patients overestimate benefits”) but only where $E > C = 0 > R$. In other words: When decisionmaking patients incur negligible costs in the choice to use a

product, then in instances where the choice is between an active course of therapy and ‘doing nothing’, the model suggests restrictions are most likely to do good only where the active therapy is expected to be beneficial but is outright harmful. Given different expectations about the active therapy, a restriction would either reduce or have no effect on patient welfare.

This result is intuitive, if perhaps not completely obvious. At first blush, it suggests that the FDA is on the right track when it seeks to restrict products that are absolutely ineffective or unsafe (“absolutely,” that is, relative to ‘doing nothing’) as opposed to products that patients tend to misjudge. But a myriad of real-world complexities are relevant and are unaccounted for in the model. Most obviously, often patients have not two but rather multiple courses of therapy from which to choose, and at those times the relevant opportunity cost to using Product A may not be the do-nothing outcome but would rather be the foregone outcome from using Product B. In the multiple-choice setting, effectiveness and safety relative to other products, as well as relative expectations, are important. As compared to the two-choice setting, it is distressing to consider the case of a misguided patient missing out not on the do-nothing therapy but on an absolutely beneficial active therapy. However, as compared to the two-choice expectations gap ($E = E_A - E_0$), the relevant expectations gap when two active therapies are under consideration ($E' = E_A - E_B$) must be smaller, and therefore a less restrictive intervention ($I' < I$) is necessary to effect the desired switch.

I will briefly discuss three other real-world complexities. First, treatment decisions very often can be characterized as being made not by a patient but by a doctor.²³ While Barros says doctors err in their selection of therapies—“Doctors tend to adopt too early and too fast, as signal of their quality, and as they bear no financial cost of decisions (and not do the patients if insured)”—he does not say that doctors also tend to overestimate the benefits of drugs. If doctors do not tend to overestimate benefits, then prescription requirements address the problem at least as well as does pre-market approval. Second, probably no drug delivers a consistent effect in every situation, as patients differ and each patient changes over time. One should of course ask how it is that the government alone is supposed to come by good knowledge of expectations and costs in a given situation, to say nothing of the less-knowable ‘real’ effects a drug will have—or, if one assumes it impossible for the government to tailor its interventions to the levels appropriate for each situation, one should ask how the beneficial effects that a general intervention may have on some situations are supposed to outweigh its negative effects on other situations. Third, any substantial restriction is sure to affect the formation of expectations. In some situations, possibly in most, a ban could prevent a patient from

²³ “In my own practice, whenever I tried to review a list of possible horrors [side effects] with a patient before starting a new treatment, the response was always the same: ‘Whatever you say, Dr. Avorn. I trust your judgment.’ This wasn’t because I had infallible therapeutic acumen, nor because my patients were unusually passive or gullible. It’s just that this is the most common patient response when these rare conversations do occur. *Of course* drugs can cause terrible side effects. Our patients expect that we will know all about this and avoid exposing them to unnecessary dangers as we care for them. With that faith, they will daily ingest several complex chemicals as we command in order to rearrange their most basic cellular functions. This trust is humbling and a little terrifying” (Avorn 2004, 166, emphasis in original).

forming a high E with regard to the banned product, but sometimes not; perhaps a patient or doctor who expects low-value products to be banned ends up with a tendency to overestimate the value of unbanned products. And there are other, nonrestrictive ways to affect directly the formation of expectations, e.g., via the generation and dissemination of information. The imposition of a restriction might be particularly pernicious if there is a natural tendency for medical professionals and patients to learn about a drug over time and form better estimates of its value; then, whatever short-run benefits the restriction yields might be outstripped by losses over the long run, as the restriction may well remain stuck in place politically even though its rationale has dissipated.²⁴

* * * * *

As mentioned above, Barros says Yes when asked if doctors systematically err when selecting and prescribing therapies: “Doctors tend to adopt too early and too fast, as signal of their quality, and as they bear no financial cost of decisions (and not do the patients if insured).” Barros implies that patients are drawn to physicians who are early adopters of new treatments. If Barros’s concern is that patients err by pressuring physicians into prescribing new drugs too soon, I assume he would have said something to that effect—thus I interpret him instead to mean that patients’ use of early adoption as a signal of physician quality is itself error-generating. Would Barros hold that pre-market

²⁴ In the terms of the formal discussion, this is to say: As E gets closer to R, it becomes less likely that $E > C > R$, which is the only ordering in which the restrictions are beneficial.

approval corrects this error by reducing doctors' opportunity to compete on early adoption? If so, how would he know? Pre-market approval has existed in something like its current form since 1962 (or earlier²⁵); if there evidence that inappropriate physician signaling via early adoption was a greater problem in, say, 1952, than it is today, Barros does not provide it. Furthermore, how are analysts supposed to know that patients inappropriately weight early adoption in their evaluations of physician quality? Surely a physician's propensity to adopt new drugs quickly is not the lone factor in patient choice—and, to whatever extent that factor *is* weighed, it may be useful or appropriate.²⁶

²⁵ Carpenter (2010, 121 n.3, 149-156, 183-188) and others have argued that the FDA had a de facto efficacy standard for several years prior to the Kefauver-Harris Amendments.

²⁶ Analysts have linked reputation to early adoption, but there are differing speculations as to the direction of causality and whether the variation is direct or inverse; also, a relevant distinction is drawn between general practitioners who make diagnoses and specialists who perform relatively well defined procedures. Navathe and David (2009, 293) theorize that "Patients select physician specialists primarily through formal networks (e.g., primary care networks, insurers, etc.) in which referrals play an important role. [...] The mechanism through which physicians accumulate patient volume is attracting referrals from their peers based, in part, on their perceived quality. Case difficulty (e.g., patient severity) and outcomes are the most observable signals colleagues receive about a physician's quality and therefore the most important determinants of reputation among peers." Navathe and David's model "predicts...that a new technology that improves the probability of success is adopted more rapidly by high peer reputation surgeons than by low peer reputation surgeons" (2009, 291). According to Navathe and David, then—at least for specialists—treatment outcomes drive peer reputation, which drives early adoption. Cf. Smythe (2002, 103-104), who considers "the reputation a physician establishes amongst her pool of potential customers, *not* the reputation a physician establishes amongst her potential competitors." In developing a model "designed to address a physician's optimal extent of adoption over time," Smythe argues in part that "Uncertainty over the impact on reputation that use of an innovation will have may lead physicians initially to adopt at less than full extent. This is driven by the durability of reputation, the physician's aversion to risk, and the ability to acquire information which enables a more informed technology choice in the future."

Physicians also face the choice of when to adopt new non-drug forms of treatment, such as surgical procedures. In a widely assigned textbook, Charles Phelps writes:

In contrast to the considerable regulation of drug safety and efficacy, no comparable regulation exists for the promulgation of new “treatments” or the assessment of previously used treatments. In this context, *treatments* refers to both surgical procedures and “strategies” for treating patients that do not involve surgery. This creates an odd schizophrenia in the production of knowledge and in the likelihood that a new treatment innovation will reach the market. Drug regulation in general, but particularly the pre-1984 rules, inhibits market entry. Nothing inhibits entry of a new surgical technique, however. This distorts the economic incentives regarding these alternative forms of therapy, probably tipping us toward “too much surgery” and not enough pharmaceutical treatment. (Phelps 2012, 465-466)

That there is an opportunity for physicians to signal their quality by adopting non-drug treatments early would, I imagine, diminish the effectiveness of any effort to dampen unfortunate physician signaling by regulating only drug treatments. Study might clarify the matter, and that sort of study would probably be in order were one to propose such an effort as a remedy to the problem of such signaling.

In addition to systematic error and uncertainty *per se*, Barros offers one more sense in which he believes imperfect information to be a source of market failure: “Companies have more information about the products and may use it strategically.” Presumably, Barros means that (1) manufacturers will conceal negative information about their products. I imagine that he would further argue that consumer and doctor skepticism cannot be counted on to balance out that concern because of (2) patients’ tendency to “overestimate benefits” and (3) doctors’ tendency “to adopt too early and too fast.” While the combination of these three numbered worries can seem ominous, the only numbered worry that applies specifically to new drugs is (3), the doctors’ bias toward early adoption. As shown above, Barros claims that the doctors’ bias results from a subtle signaling problem in the market for physicians, a problem for which I could not find unambiguous evidence in the literature (see *supra* note 26). And, again, it is hard to see how well pre-market approval would work to remediate this supposed problem.

Barros also cites public-goods aspects of knowledge as a source of market failure. To the question “*Say the policy that requires pre-market approval was eliminated and, in its place, a policy was implemented allowing new pharmaceuticals/devices and initially classifying them as requiring a doctor’s prescription (pending a review process to consider dropping the prescription requirement). Do you think such a liberalized system would be superior to the current system?*”, Barros responds No and gives this reason:

Knowledge about the new pharmaceutical products is a public good, and a liberalized market does not have the right provision incentives.

I presume that when Barros invokes “the right provision incentives,” he is referring simply to the classic conditions for blackboard perfection. Also, he says uncertainty *per se* constitutes a market failure, writing:

Obtaining knowledge to reduce uncertainty has aspects of a public good.

Barros then confronts question 18b: *You indicated that public-goods aspects of knowledge are a source of the market failure that justifies the policy requiring pre-market approval. Do you think that this source of market failure would be better addressed with a policy that subsidizes the generation of knowledge, e.g., via the National Institutes for Health?* He answers No, but when asked “Why not?” he muddies the waters (my emphasis):

I see the pre-market approval as minimum quality standard that needs to be enforced. This requires information and enforcement power. **The subsidization of the generation of knowledge provides the information** but not the enforcement of minimum quality standards.

Barros thus seems to acknowledge that a subsidy could address the public-goods aspects of obtaining knowledge or reducing uncertainty. In the context of a response to question 18b, his introduction of the notion of a “minimum quality standard” reads as a non sequitur. Not here and not elsewhere in his responses does Barros directly connect any of his market-failure ideas to the remedy of a “minimum quality standard,” yet here he speaks as if that remedy is the foregone policy conclusion to which those ideas lead us.²⁷

Oddly, the ‘need’ for a minimum quality standard is not Barros’s explanation for his rejection of the reform of question 22b—*As compared to the current system, would you favor making approval of a new drug automatic upon completion of the safety and efficacy testing processes specified by the FDA, regardless of what those testing results turned out to be?* He leans on an informational effect:

The extra information brought in the process of approval is also relevant.

²⁷ The phrase “minimum quality standard” calls to mind the model built by Carl Shapiro (1983), which posited that economic gains can be had from the imposition of such a standard. Perhaps this is what Barros has in the back of his mind, though he does not say. If so, next steps in developing his argument would include comparison between the theoretical net gains (which accrue to consumers of ‘high-quality’ products, at lesser expense to the would-be consumers of ‘low-quality’ products) and the costs of enforcement, discussion of knowledge effects and distributional matters, acknowledgment of public-choice hazards, etc.

Extra information is always potentially relevant, of course. The gist of the proposal is to reform the law so that knowledge generation *is* required but that approval is not *otherwise* withheld. Whatever is the level of research, testing, and analysis deemed sufficient, the question re-emerges: Why not require the generation of knowledge without otherwise withholding permission? Barros's remark does not address the elemental question.

Cornelis Boersma

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Boersma supports the pre-market approval policy, but not strongly. He holds that several market failures justify pre-market approval, including imperfect information. He says that patients systematically err in “several” ways when coping with health or treatment uncertainties but gives only one example, “patients’ drug persistence in general.” Regarding medication, the term *persistence* “refers to the act of continuing the treatment for the prescribed duration. It may be defined as ‘the duration of time from initiation to discontinuation of therapy’” (Cramer et al. 2008, 44). It is difficult to guess

what connection, if any, Boersma would draw between persistence and pre-market approval.

When asked whether doctors systematically err when selecting and prescribing therapies, Boersma says Yes:

Not only the evidence and importance of health gains but also financial aspects (e.g. profits next to drug prices) are weighted in their choices. Not always evidence based (e.g. strictly following market approval vs. off-label). Among other points, routine decisions on drugs and devices in stead of (guideline) recommended and/or evidence-based. This can lead to ‘trial-and-error’ treatment strategies[.]

I read Boersma’s first sentence as implying that a doctor’s profit incentive may not be perfectly aligned with his judgment about prospective health gains—a concern that arises from specialization of labor, which more-or-less requires that each of us is grossly ignorant of the particulars of all fields besides our own. Economists generally agree that this gross ignorance is not problematic for exchange whenever buyers are able readily to evaluate the quality of finished products or services. In a famous paper, Arrow (1963, 949-951, 965-966) argued that the extraordinary lengths to which physicians go in demonstrating trustworthiness and competence can be explained by the difficulty consumers have in evaluating medical services. The idea is that a consumer will readily

purchase two-by-fours from a ruthlessly profit-focused seller because the quality of the product is apparent, but a consumer will purchase medical diagnosis and treatment services only from someone trusted to put the consumer's health first because a profit-focused physician may find leeway to 'diagnose' and 'treat' nonexistent maladies.²⁸ I assume Boersma would make the valid point that consumers' insistence upon trustworthiness may not entirely resolve this matter. Could pre-market approval close whatever gap exists, or serve in any way to beneficially constrain doctors who try to profit through actions that run at least somewhat counter to patient interests?

Doctors can sometimes profit directly by administering or prescribing drugs: they are able to mark up the cost of drugs that they administer themselves, and while pharmacies receive most of the business stemming from prescriptions, some dispensing is done by doctors' offices. And perhaps there is pressure put on doctors by other players in the industry—e.g., a hospital might pressure its doctors to consider financial aspects of drug therapies. More notoriously, doctors can profit receive substantial gifts or opportunities from drug producers, and much evidence shows that these benefits impact doctors' attitudes and prescription practices (Wazana 2000).

But remedial interventions other than pre-market approval could, and do, apply much more directly. For example, physicians are currently prohibited from receiving

²⁸ Competition among physicians can mitigate this problem; it is a common wisdom among newly diagnosed patients to seek a 'second opinion.'

payments in return for any prescription (or referral, or other product recommendation) that will be reimbursed by Medicare, Medicaid, or other federal programs. Lawsuits and investigative journalism have done much to publicize financial relationships between doctors and drug companies (Ornstein et al. 2011). Implementation of the federal Physician Payments Sunshine Act mandating disclosure of such relationships, called the “Open Payments” program, began in 2013 (Centers for Medicare & Medicaid Services 2012; Agrawal 2014).

In contrast to these regulations and campaigns, it is not obvious how pre-market approval is supposed to constrain a profit-seeking physician. First, think about a physician who makes money off any prescription. A corrupted physician who is able to make a false diagnosis can simply proceed to recommend or prescribe a drug approved for that condition or, indeed, any approved drug. Then, imagine a doctor who lacks power to alter a diagnosis, perhaps because there is a clear patient history or because other knowledgeable observers are currently involved, but the doctor is supposed to select treatment. Such a doctor also can prescribe or recommend any approved drug. Perhaps the doctor would be somewhat more open to challenge by observers were she to prescribe off-label rather than on-label, but a regulator could impose labeling requirements without pre-market approval (see Variant #2 in Table 1), plus it is difficult to see why the “on-label”/“off-label” regulatory classification would trigger many challenges in excess of those that observers would have mounted simply because the doctor in question is prescribing a drug that does not suit the diagnosis. Meanwhile, conceivably it is the case

that pre-market approval tends to foster consumer complacency—all the drugs you can buy are guaranteed safe and effective, no?—and thereby dampens observer propensity to verify, investigate, or challenge a doctor’s treatment recommendations.²⁹ So it seems doubtful, or at least not in evidence, that pre-market approval does much to constrain the physician who profits any time he makes a prescription.

Now imagine a physician who wants to profit by prescribing or recommending a specific drug. For pre-market approval to be an effective constraint, the drug in question must be one he would not otherwise be constrained from prescribing (i.e., here we presume that observer pressures, even aided by labeling, fail to do the job), that yet is banned under pre-market approval. In this situation, with observer pressures on his practice being so weak, why wouldn’t one expect the profit-oriented physician simply to shift his tactics to some other pursuit, such as performing unnecessary procedures or insisting on more visits? Perhaps it is because the drug in question represents a particularly lucrative opportunity, e.g., via inducements from a manufacturer, but the anti-kickback and disclosure laws would seem sufficient at deterring that sort of relationship, and indeed superior considering that they would apply to all drugs and not just to those that would be banned under pre-market approval.

²⁹ I am unaware of any non-anecdotal evidence demonstrating the pervasiveness of such an attitude, but consider this remark from a consumer advocate upon the fact that certain unapproved drugs remain commercially available because of incomplete enforcement by the FDA: “People tend to assume that if a drug is available in the U.S., it’s safe and it works” (quoted in Harrar 2009).

* * * * *

Boersma (apparently) sees systematic error in physicians' failure strictly to follow FDA approval decisions when selecting therapies—"Not always evidence based (e.g. strictly following market approval vs. off-label)"—but he would only beg the question were he to offer this as a justification of pre-market approval itself. Boersma also sees systematic error whenever physicians make "routine" decisions instead of following "evidence" or a "guideline." Whether routines economize appropriately on knowledge or not, pre-market approval could only prevent physicians from exercising routine choice of unapproved drugs; pre-market approval could not prevent doctors from continuing to follow routine within the set of approved drugs.

Boersma is then asked question 11b: *Say the policy that requires pre-market approval was eliminated and, in its place, a policy was implemented allowing new pharmaceuticals/devices and initially classifying them as requiring a doctor's prescription (pending a review process to consider dropping the prescription requirement). Do you think such a liberalized system would be superior to the current system?* He says No, yet when asked "Why not?", he offers no reasons but is content merely to describe his favored policy:

The drug and medical device market should definitely be regulated to a certain extent and is therefore not suitable for liberalized system. This is

due to different supply/demand framework for health care versus other product markets. In my opinion, a combined regulation/liberalization system should be prefer[r]ed. Pre-market approval should go hand in hand with liberal policy after approval to also find evidence for more heterogeneous populations (other than populations in randomized clinical trials). Of course, the latter should be evidence dependent and requires (strict) monitoring to evaluate ‘real-life’(cost-)effectiveness and safety leading to evidence-based medicine decisions.

It is very hard to infer the basis on which Boersma favors this “combined regulation/liberalization system.” And I wonder what “liberal policy after approval” is supposed to denote. After approval, a drug can enter the market; it is, well, *approved*. I doubt that Boersma meant to say he favors further liberalization of the rules governing approved drugs, e.g., the dropping of prescription requirements or the liberalization of manufacturer speech; I am more inclined to interpret his endorsement of “liberal policy after approval” as a sanctimonious affirmation of the status quo.

In addition to patient and doctor erring, Boersma offers this sense in which he believes imperfect information to justify pre-market approval:

Clinical trial outcomes are limited to specific/selected patient populations. Therefore, interpretation and translation of outcomes

((cost-)effectiveness & safety) to ‘real-life’ practice is often difficult and not (always) evidence based. Valuation of existing information/evidence gives the opportunity to make health care decisions with considering existing uncertainty.

Boersma seems to be saying that pre-market approval is justified *because* the knowledge gained from clinical trials is not perfectly applicable to “‘real-life’ practice.” He characterizes pre-market approval as merely “[v]aluation of existing information/evidence” and suggests that the policy frees practitioners to cope with less uncertainty.

Expert evaluation of trial data certainly does reduce the cognitive burden on doctors and consumers, as acknowledged in my comments on Arrow’s concern that “Information is difficult to... understand,” but again, pre-market approval is distinctive not for evaluation but for (lifting) prohibition. While the trial-analysis experts may be better equipped to deal with some evidentiary complexities, physicians and consumers have local knowledge and incentives that the trial-analysis experts do not. The existence of local knowledge and incentives means there are tradeoffs at the margin and no clear case for the trial-analysis experts’ views to supervene those of the consumers or physicians (local knowledge and incentives were emphasized by Smith as he propounded the presumption for liberty; I collect relevant quotations in Appendix A). Therefore, as an economist I fall back on our typical course of analysis, in which a division of knowledge

is considered to be a near-universal phenomenon, not a market failure (Higgs 1994, 5-10). The division of knowledge could be explored with a model in which some pharmaceutical expert is presumed to have relevant expertise, while consumers are each ‘expert’ in their own ‘fields’ (medieval French history, bus driving, *one’s own medical history*, etc.), and everyone knows that such a division exists. In this model, when it comes to a typical consumer’s medical questions, we would probably hope and expect that the consumer would place appropriate trust in the pharmaceutical expert’s judgment (Klein 1998a, 549-551). If it were shown that, when weighing decision factors, consumers systematically erred by placing too little or too much trust in the expert’s recommendations, then the case for some government interventions might be buttressed.³⁰

Boersma said in response to question 5b that public-goods aspects of knowledge can justify pre-market approval. Later, when asked in question 18b whether that source of market failure “*would be better addressed with a policy that subsidizes the generation of knowledge, e.g., via the National Institutes for Health?*”, he said Yes. In response to the next question, “*Do you think the policy that requires pre-market approval induces the generation of more knowledge about the new pharmaceutical than there would have been in the absence of the policy?*”, he said Yes. Boersma then considered the reform proposed by question 22b: “*As compared to the current system, would you favor making approval*

³⁰ “Given that trust carries costs as well as benefits, what is needed is to achieve an optimal level of trust” (Buchanan 2000, 190).

of a new drug automatic upon completion of the safety and efficacy testing processes specified by the FDA, regardless of what those testing results turned out to be?” He said No, but qualified that response, writing: “Reporting on drugs and devices from a FDA perspective provides us with an independent and transpar[e]nt vie[w] on (not) approved products.”

I see little reason to presume that an FDA panel is more “independent” than any given individual or party.³¹ The Administration is dependent upon both the U.S. Congress and the pharmaceutical industry for its funding, and FDA power depends on the maintenance of its reputation among a multitude of audiences (Carpenter 2010). In surveys, a substantial share of FDA scientists claim to have encountered political interference with their own work (Union of Concerned Scientists 2012; 2006). Many individual doctors or analysts might be considered at least comparably independent from economic and political pressures, indeed perhaps far more independent. Boersma’s assertion that the FDA is simply “independent” is similar to Arrow’s talk of “interested parties” and “the right incentives.” Also like Arrow, Boersma does not seem to be particularly aware that the FDA suppresses, rather than shares, information about unapproved products.

³¹ The political system does succeed in producing environments with varying degrees of independence from electoral pressures (Devins 1993), and in that sense the FDA might be judged among the more independent federal bureaus. But the relevant comparison is between the FDA and others who may conduct analysis of pharmaceutical quality, not between the FDA and the Federal Reserve or the Department of Defense.

It is also not clear in what sense, or relative to what alternatives, Boersma judges the FDA (or its processes, etc.) to be “transparent.” At least some other observers have judged that it could be more so: in May 2010—that is, subsequent to Boersma’s completion of the questionnaire—an FDA “Transparency Task Force” proposed 21 changes to current policy (FDA TTF 2010, 1).

Boersma goes on to say: “In case of automatic approval, it would be necessary to introduce the concept of ‘risk-sharing’ to make manufacturers (rather than government) responsible for the market behaviour and consequences in terms of (cost-)effectiveness, safety profile and budget impact related to health care professionals’ choices on (new) drugs and devices.” Boersma does not say if or why he would prefer pre-market approval to this alternate regime (safety and efficacy testing by the FDA, automatic approval, and “risk-sharing”).

The questionnaire then probes Boersma’s belief (indicated in question 5b) that the government has superior ability to assure safety and efficacy. Question 24b asks, “*Does that superiority stem from the FDA having special expertise in evaluating safety and efficacy?*” Boersma says Yes but immediately backtracks:

May be not inferior but more individualized judgement/evaluation of safety and efficacy, rather than based on a variety of expertise within FDA expert panels.

Here Boersma characterizes the basis—“a variety of expertise”—upon which he sees the FDA forming its judgments, but he offers no corresponding characterization of the basis upon which patients or doctors would form their “individualized” judgments. But, judgment is merely the bringing of some decisionmaking process to closure. That we observe the FDA’s process to involve a group of people gathered together,³² while some patient or doctor may not actively consult with another person, does not speak to whether a “variety of expertise” is or is not part of the knowledge that either party actually uses as its basis for judgment. One might imagine an instance of FDA decisionmaking in which a variety of experts see their views trumped internally by political pressure,³³ and then one might imagine an ‘individual’ doctor deciding on a prescription after reading a meta-study published in a peer-reviewed journal by a team of researchers working at a prestigious university. A contrived example, of course, but it exposes Boersma’s

³² Under the FDA Revitalization Act of 1990, FDA has been attempting to consolidate its employees at fewer locations. In testimony aimed at securing funding for the consolidation project, an FDA deputy commissioner told Congress in 1996 that “FDA is scattered in more than 40 buildings—many with outdated and unacceptable laboratories—in 18 different locations” (Holston 1996). Staff from the Center for Drug Evaluation and Research started moving onto a campus in Montgomery County, Maryland, during 2003. The FDA expected more CDER staff to move onto the campus in 2014 (FDA.gov 2011).

³³ A recent example is the rejection by HHS Secretary Kathleen Sebelius of FDA’s recommendation that a prescription requirement on the contraceptive Plan B One-Step be removed (Sebelius 2011; Harris 2011). Specifically on the matter of Presidential “directive authority” over executive branch officials, see Kagan (2001).

attempted distinction as trivial: We are all already aware that FDA employs some experts.³⁴

Following is question 26b, “*Would you say that impartiality or commitment to the public good are sources of the government’s superior ability to assure safety and efficacy?*” Boersma says Yes. He then is asked, “*In what ways does the FDA’s impartiality or commitment to the public good render it superior to doctors and patients in judging safety and efficacy?*”

- Wide variety of expertise - Independent view - No (direct) financial interest of experts - Critical and transpar[e]nt - Etc

This only reiterates Boersma’s earlier points, which I have taken up above.

Boersma describes (in question 5b) an “Other” source of market failure justifying pre-market approval as “gives guidance in comparing treatment options (e.g. less off-label use expected).”³⁵ If this is to say that the FDA’s evaluation itself represents useful

³⁴ Thomas McGarity and Sidney Shapiro (1980, 840-844) assert that the variety of medical expertise is far greater outside the FDA than within it, and they say FDA generally cannot leverage that outside expertise in its decisionmaking processes.

³⁵ Where Boersma puts the existence of “off-label” prescribing into his justification for the very classification of some uses as “off-label,” there is again a hint of begging the question, as well as an excellent illustration of how difficult it is, in the midst of the reality of pre-market approval, for one to conduct a thought experiment about its absence.

information, the question is why that usefulness would be diminished if the evaluation occurred within a liberalized regime, e.g., as in Table 1's Variants #1 and #2.

At the questionnaire's end, Boersma offers this general commentary:

Regulatory systems - such as FDA pre-market approval - for drugs and medical devices based on efficacy & safety are required to judge these products, provide information and translate existing outcomes evidence to guide health care professionals. Uncertainty issues will always exist due to differences between controlled settings (selected populations) and 'real-life' settings (heterogenous populations. Several methods exist to show or value uncertainty around (cost-)effectiveness/safety outcomes. Therefore, these methods can contribute to decision-making processes (e.g. to decide on timing of a decision (here, approval) or to decide on additional requirements for additional research to reduce uncertainty). Also, follow-up monitoring of 'real-life' (cost-)effectiveness and safety profiles should be recommended to give guidance in (evidence-based) treatment choices.

This statement might be condensed to the following: 'Regulatory systems—such as FDA pre-market approval—are required to judge these products, provide information and translate existing outcomes evidence to guide health care professionals. Uncertainty

issues exist. Several methods exist to value uncertainty, and these methods can contribute to decision-making processes (e.g., approval).’ Paraphrased tightly, it becomes: ‘Uncertainty exists, it can be valued, and those valuations should be used to guide approval decisions.’ But the question at hand is why a regulator should *make* approval decisions, not what should guide approval decisions. Not only does Boersma evade the question, he refrains from drawing any distinction between pre-market approval and other “regulatory systems,” even though pre-market approval does much more than “judge these products, provide information and translate existing outcomes evidence to guide health care professionals.” In comparison with Arrow, Boersma exhibits a stronger form of denial in that he does not face up to the existence of a coercive element in drug-approval policy.

Don Husereau

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Husereau supports pre-market approval, but not strongly. He says that both consumers and doctors err systematically, attributing the same set of biases to both groups:

Information Bias - Leads to inappropriate use of diagnostic testing and harm (Baron, Beattie, Hershey , 1988 and others) Attribution bias - Consumers will incorrectly mental account positive and negative features (Shafir, 1992) Omission bias - Consumers will avoid therapies that benefit Other violations of expected utility related to personal choice under uncertainty - (Tversky and Kahnemann, 1981, 1992; Allais (1953) then Slovic and Tversky (1974) then Keller (1985).

Below I examine these citations for their relevance to medicine and to pre-market approval. I will follow Husereau by grouping the citations under four headings. Under each heading, I attempt to answer three questions: *What is the bias* or systematic error identified in the cited work? *Does the bias (or error) affect patients or doctors* when selecting therapies? *Is pre-market approval a suitable remedy for the bias* or error?

“Information bias”

Citation provided: Jonathan Baron, Jane Beattie, and John Hershey (1988)

What is the bias?

“Subjects evaluated questions as worth asking even when there is no answer that can change the hypothesis that will be accepted as a basis for action” (Baron et al. 1988, 88).

Baron, Beattie, and Hershey observed the bias in a minority of the few students that they tested, though “a majority of the 33 subjects given these problems answered them correctly” (1988, 103-104). At least one of the students exhibiting the bias was able to overcome it after only a brief prompt (ibid., 105).

Does the bias affect patients or doctors?

“Much of the thinking that occurs in daily life and in professions such as science and medicine involves the formulation and testing of hypotheses. Given a set of one or more hypotheses, there are often several questions that might be asked—several pieces of evidence that might be requested—to test these hypotheses” (ibid.).

In their literature review, Baron, Beattie, and Hershey write that “[s]everal accounts have suggested that the use of an information heuristic might contribute to the performance of medical tests that are expensive, dangerous, and unnecessary” (ibid., 90).

Is pre-market approval a suitable remedy for the bias?

To apply the Baron et al. model in the context of pharmaceuticals, I will imagine there is a doctor with a given hypothesis as to which drug he should prescribe. What may happen if the doctor “evaluate[s] questions as worth asking even when there is no answer that can change the hypothesis”?

First, there would be simple waste, as the doctor uses up time or resources in the asking of superfluous questions that will not alter her initial hypothesis as to which drug she should prescribe. So a cheap remedy to information bias could save some money by reducing waste. But it could also be the case that the superfluous questions ‘crowd out’ questions that could change the hypothesis for better or, possibly, for worse. Thus a remedy to information bias could possibly improve prescription decisions, but only if it is the case that doctors relieved from information bias will proceed to ask good questions.

What happens when pre-market approval is introduced to this model of prescription-making in which a doctor has an initial hypothesis and then formulates questions? Pre-market approval is a sweeping policy that brings across-the-board change in ideas and practices, but I say the cleanest and best way to operationalize it within this model would be to characterize its restrictions upon choice as primarily impacting the initial hypotheses (by prior removal of many possible choices from consideration) while its conceptual and informational effects primarily impact the formation of questions.

Could it be the case that pre-market approval improves prescription decisions by restricting choice and thus shaping the space from which initial hypotheses are drawn? Maybe, but Baron et al. (1988) is about hypothesis *testing*. Information bias is present when, given an initial hypothesis, someone who seeks to evaluate the hypothesis places value on information useless for that purpose. Information bias could possibly be used to justify efforts to guide the questions doctors ask—and, certainly, via its conceptual and

informational effects, pre-market approval does this—but information bias is unconvincing as a justification for the replacement of one initial hypothesis with another, as is effectively done by pre-market approval’s ban on unapproved products.³⁶

“Attribution bias”

Citation provided: Husereau wrote “Shafir 1992,” but my research suggests that he likely intended to cite Eldar Shafir (1993) as evidence for his claim that “Consumers will incorrectly mental account positive and negative features.”

What is the bias?

“In line with the principle of compatibility, according to which the weighting of inputs is enhanced by their compatibility with output, the positive and negative dimensions of options (their pros and cons) are expected to loom larger when one is choosing and when one is rejecting, respectively” (Shafir 1993, 546).

³⁶ Husereau cited Baron et al. (1988) with regard to “information bias,” but it is worth noting the discussion in that same paper of “congruence bias”: “Subjects overvalued questions that have a high probability of a positive result given the most likely hypothesis. This bias was apparently reduced when alternative hypotheses or probabilities of negative results are explicitly stated. [...] The use of this heuristic would seem to be especially likely when people have only a single hypothesis in mind” (Baron et al. 1988, 88-89). If doctors’ question-asking or evidence-seeking processes are otherwise healthy and productive, then, in light of congruence bias, efforts to occlude or deny the existence of alternatives to an initial hypothesis may be unfortunate and counterproductive.

Shafir presents experimental evidence of the bias under three headings: “Binary Problems,” “Nonbinary Problems,” and “Choice Sets and Framing.” The bulk of his evidence comes from the binary problems:

Each problem presents a choice between two options: an option with more positive and more negative features (henceforth, the enriched option) and an option with fewer positive and fewer negative features (henceforth, the impoverished option). [...] Each problem was presented to two groups of subjects: one group was asked to choose (award or indicate a preference for) an option; the other group was asked to reject (deny or give up) an option.

Let Π_c and Π_r denote, respectively, the percentage of subjects who choose and who reject a particular option. If choosing and rejecting are complementary (i.e., $\delta = \lambda$), the sum $\Pi_c + \Pi_r$ should equal 100. According to the rationale outlined in the previous section, on the other hand, we should expect the enriched option to be chosen and rejected more often than the impoverished option. According to this prediction, the value of $\Pi_c + \Pi_r$ should be greater than 100 for the enriched option and, consequently, smaller than 100 for the impoverished option. (ibid., 549)

Shafir generated experimental data using seven binary problems and two groups of subjects for each problem, finding these values of $\Pi_c + \Pi_r$ for the enriched options: 119, 115, 110, 125, 117, 117, and 113. Shafir summarized these values when reporting results from an alternate study design in which a subject would receive both versions of a problem:

[T]wo problems [Problem 4 and Problem 5] were replicated in a within-subject design. Two hundred and forty-eight subjects received both the choice and the rejection versions of these problems. Half the subjects received both versions of Problem 4; the other half both versions of Problem 5. The two versions appeared in a booklet, separated by numerous unrelated problems in between, with their order of occurrence counterbalanced across subjects. Because there were no significant differences between problems or orders, the data were combined. We call a subject consistent if, having chosen one lottery, he/she then rejects the other, and vice versa. A subject is inconsistent if he/she both chooses and rejects the same lottery. Whereas a standard analysis based on error predicts that inconsistent subjects will be roughly equally distributed among the two options, the present thesis predicts that a majority of inconsistent subjects will have both chosen and rejected the enriched rather than the impoverished option. Averaged over problems, 22% of the subjects exhibited inconsistent preferences (24% and 20% for

Problems 4 and 5 respectively). This corresponds quite well to the inconsistency rate implied by the between-subject manipulations above. More importantly, in line with the compatibility hypothesis, a significant majority of inconsistent subjects chose and rejected the enriched rather than the impoverished lottery (74% vs. 26%, $p < .01$). (ibid., 551)

I interpret Shafir as suggesting that, on average, about 10% of students exhibited inconsistent preferences *because of* compatibility effects, while another 10% or so exhibited inconsistent preferences for whatever other reason, and roughly 80% exhibited consistent preferences.³⁷

Does the bias affect patients or doctors?

Shafir (ibid., 554) thinks it may: “As pointed out by Bursztajn et al. (1991), clinicians make treatment decisions prospectively, with the hope of improving the patient’s health, whereas judges hearing malpractice cases must address such decisions retrospectively, after a harm has occurred. Thus, the courts tend to be more attuned to the

³⁷ The calculation I am making here is: Assume that those inconsistent subjects not decisively affected by compatibility are evenly distributed, while other inconsistent subjects choose the enriched option. Given that 26% of inconsistent subjects chose the impoverished option, we thus assume another 26% are not affected by compatibility. So the affected are 48% of the inconsistent 22%, or 10.6%; the unaffected but inconsistent are 52% of 22%, or 11.4%; and the consistent are 78%.

potential harms of the treatment than to its benefits, relative to the doctors whose main concern are the potential benefits despite the risk of harm. One possible implication of this disparity is a greater propensity on the part of doctors to choose enriched treatments—ones that promise a variety of potential improvements—and a greater tendency on the part of the courts to find fault with the very same treatments, because of their more numerous potential harms.”

Is pre-market approval a suitable remedy for the bias?

Assume for the moment that FDA decisions do not suffer from attribution bias, while doctors’ and consumers’ decisions do. Whatever drugs are banned, doctors and consumers selecting from the set of legal treatments are still likely to overconsume relatively “enriched” legal treatments and underconsume relatively “impoverished” legal treatments. So even if FDA could identify enriched treatments and were to impose upon them a higher bar for approval, it would remain the case that some legal treatments are enriched relative to other legal treatments, and these would tend to be overconsumed whenever doctors or consumers find themselves to be comparing treatments. And while those treatments that would have won approval under an enrichment-neutral policy but fail to clear the higher bar would no longer be overconsumed relative to their merit, they now would not (legally) be consumed at all.

By contrast, to the extent that FDA would allow enriched treatments to remain legal but would impose restrictions (such as prescription requirements) or other costs³⁸ upon the choice of those treatments by patients, it might do somewhat better at hitting a sweet spot. And what Shafir sees as an already-existing “tendency on the part of the courts to find fault with [enriched] treatments” would seem to provide a similar balancing effect upon physician decisions.

A nonrestrictive policy of doctor education might also do better than pre-market approval. Would it not be foolish to entrench politically a far-reaching apparatus that blocks voluntary transactions because doctors are biased, only to turn around and see medical schools across the country start to successfully train students about their own biases and coach them in methods for countering the biases? The doctor-education approach, being humbler, seems to me that much more sensible when it comes to a bias that probably affects no more than one in ten doctors to start with and is most relevant to close decisions, e.g., when neither of two options under consideration is clearly superior to the other. And once the doctor-education approach is taken, then even if we remain concerned that (ten percent of) patients cannot overcome their attribution bias through

³⁸ It seems politically unlikely for a tax to be placed directly upon a drug perceived to be highly effective, as health care is a morally sensitive space and because such taxation could be seen as unfair to poorer patients. Prescription requirements and product bans are not generally viewed as unfair to the poor; however, to the extent that a product restriction or ban is circumvented by privileged groups, it can come to be seen as unfair to groups who cannot obtain the product easily or without being punished. For example, it is not uncommon to see arguments that policies and practices implementing the ban on cannabis are broadly racist (see, e.g., Levine and Small 2008; Gutwillig 2009; Dwyer 2009; Alexander 2010).

learning, prescription requirements should remedy that bias just as well as would pre-market approval.

“Omission bias”

Citation provided: None. I will proceed with a discussion of David Asch et al. (1994).

What is the bias?

“Several laboratory studies have suggested that many people favor potentially harmful omissions over less harmful acts” (Asch et al. 1994, 118).

Does the bias affect patients or doctors?

Asch et al. believe so: “Our results indicate that the bias toward omissions found in laboratory settings plays a role in some decisions not to vaccinate with DPT [the combined diphtheria-pertussis-tetanus vaccine]” (1994, 121). “[O]ur results may be meaningful for a host of other proxy decisions, including those made by surrogate decision makers for critically ill patients” (ibid., 122). “Physicians...may prefer responsibility for omissions to responsibility for commissions. Further work is necessary to determine whether this bias is present when patients make decisions about their own medical care” (ibid.).

Is pre-market approval a suitable remedy for the bias?

Asch et al. (1994) advocate two remedies to omission bias in the context of vaccination, one clearly educational and a second that is mildly manipulative but not coercive:

Baron [(1992)] found that subjects who opposed vaccination could be persuaded to vaccinate by an argument emphasizing the “Golden Rule.” The argument suggested that subjects put themselves in the child’s position and ask themselves whether they preferred a greater or lesser chance of death and whether it mattered whether these chances came about through someone’s act or omission. Of 63 subjects, 16 had said they would not vaccinate originally, but after reading the argument only six would not vaccinate. [...]

There may be other ways to reduce this bias. Physicians and public health programs might reverse the framing of acts and omissions so that the decision not to vaccinate is seen as more of an act than the decision to vaccinate [Tversky and Kahneman (1981)]. For example, pediatricians might vaccinate as a matter of course, and require special consent only if a parent refuses. (Asch et al. 1994, 122)

How might omission bias matter in the context of pharmaceutical choice? Perhaps we are to think that omission bias serves generally to dampen enthusiasm for medical interventions (e.g., procedures, use of pharmaceuticals, etc.), while regimes such as pre-

market approval serve to boost confidence in medicine.³⁹ However, it is very unclear that pre-market approval is the best means by which confidence in medicine might be increased, nor is it clear how such confidence-boosting efforts could be calibrated so as not to overshoot the mark, nor how analysts are supposed to locate that mark in the first place.

Omission bias seems more likely to be raised in a criticism of pre-market approval. The relevance there is obvious: FDA, in making a proxy decision for doctors and patients, may eschew responsibility for commissions—drug approvals—in favor of passive failures to approve.

“Other violations of expected utility related to personal choice under uncertainty”

Citations provided: Amos Tversky and Daniel Kahneman (1981); Tversky and Kahneman (1992); Maurice Allais (1953); Paul Slovic and Amos Tversky (1974); L. Robin Keller (1985)

What is the bias?

³⁹ Carpenter, Grimmer, and Lomazoff (2010) offer a model in which pre-market approval increases the confidence of consumers in the regulated market as a whole. “In making inferences about any one product drawn from the distribution...consumers will take into account properties of the distribution itself, such as expected values and uncertainty. Our argument, in summary, is that approval regulation shapes this general distribution” (ibid., 390).

Tversky and Kahneman (1981) address the effects of framing on decisionmaking.

The first two sentences of their Summary are:

The psychological principles that govern the perception of decision problems and the evaluation of probabilities and outcomes produce predictable shifts of preference when the same problem is framed in different ways. Reversals of preference are demonstrated in choices regarding monetary outcomes, both hypothetical and real, and in questions pertaining to the loss of human lives. (Tversky and Kahneman 1981, 453)

Tversky and Kahneman (1992) emphasize differences between patterns of decisionmaking followed by subjects in experimental settings and those patterns that some analysts would have expected the subjects to follow. The body of their paper begins:

Expected utility theory reigned for several decades as the dominant normative and descriptive model of decision making under uncertainty, but it has come under serious question in recent years. There is now general agreement that the theory does not provide an adequate description of individual choice: a substantial body of evidence shows that decision makers systematically violate its basic tenets. [...] Some

time ago we presented a model of choice, called prospect theory, which explained the major violations of expected utility theory in choices between risky prospects with a small number of outcomes (Kahneman and Tversky, 1979; Tversky and Kahneman, 1986). [...] This article presents a new version of prospect theory that incorporates the cumulative functional and extends the theory to uncertain as well as to risky prospects with any number of outcomes. (Tversky and Kahneman 1992, 297-298)

Maurice Allais, in the English summary of his classic ‘paradox’ article, writes:

The experimental observation of the behavior of men who are considered rational by public opinion, invalidates Bernoulli’s principle.

Four classes of facts are particularly significant in this regard:

- (i) The manner in which very prudent people behave in gambling small sums.
- (ii) The choice of risks bordering on certainty that contradicts the independence principle of Savage.
- (iii) The choice of risks bordering on certainty that contradicts the substitutability principle of Samuelson.

(iv) The behavior of entrepreneurs when great losses are possible. (Allais 1953, 505)

Here is the abstract from Paul Slovic and Amos Tversky (1974):

Many decision theorists believe that the axioms of rational choice are similar to the principles of logic in the sense that no reasonable person who understands them would wish to violate them. The present study questions that view by investigating the acceptability of a key axiom underlying expected utility theory—Savage's independence principle. Persistent violations of this axiom were observed, even after it was presented to subjects in a clear and, presumably compelling fashion. The problem of distinguishing between rejection of a decision principle and failure to understand it is discussed. (Slovic and Tversky 1974, 368)

The abstract from L. Robin Keller (1985) begins:

This paper reports an experimental investigation of the effects of three forms of problem representation on compliance with the Sure-Thing and Substitution Principles. The most common form of representation, written problem statements, was compared with two visual representations: decision matrices with each column proportional in size

to the probability of the corresponding event and tubes containing 100 labeled balls. The proportional matrices led to fewer violations of both principles. (Keller 1985, 738)

Does the bias affect patients or doctors?

None of the five studies specifically study health-care decisions, but many patients can be presumed affected. Evidence on the effects of education or training to overcome the reported bias, as might be given to doctors, is presented by two of the papers. Slovic and Tversky (1974, 372) conclude that, with regard to Savage's independence principle, "SIP is more complicated and less familiar than transitivity, so people do not accept it at first. Only after they have had ample opportunity to become acquainted with the axiom, do they appreciate its full normative impact." Keller (1985, 750) finds that "matrix-structuring training is likely to lead to even fewer violations [of the Sure-Thing and Substitution Principles] than the already reduced number of violations resulting from using pre-structured proportional matrices."

Is pre-market approval a suitable remedy for the bias?

Doctors and patients are not, generally, presented with arithmetically precise decision problems. Decisionmaking heuristics that appear irrational or unhelpful in the context of a solvable problem may be reasonable or at least not substantially harmful when applied to problems where competing interests are at play, which is to say, to most any problem with economic import. Imagine confronting problems with the form put

forward by Keller, but where the ‘experimenter’ has been replaced with a *seller*, such as a manufacturer or a doctor. What good is an ability to parse, with great precision, a numeric decision problem as it is presented by a seller? If the problem is solvable, wouldn’t a trustworthy seller—or analyst, certifier, etc.—have solved it already and be standing prepared to explain her calculations? The ability to determine who is both knowledgeable *and* trustworthy is far more valuable to patients than is the ability to solve numeric decision problems, and assessments of knowledgeability and trustworthiness cannot be formed to any very significant extent through arithmetic calculation.

Arithmetically precise problems aside, Husereau’s concern would seem to be that patient choices can be gamed, in that someone with knowledge of common biases could structure their presentations so as to be chosen even though their product is inferior. But why would only the producers of inferior products do this? Superior products should presumably still have an advantage whether marketers incorporate consumer biases into their presentations or not. It could be that heavily marketed products look better than they should relative to less marketed options such as ‘doing nothing’; notice, though, that this effect runs counter to the effect expected from omission bias, and of course no evidence exists purporting to measure the net effect from both biases, let alone all biases.

Concerns about framing of information would seem to apply to all products, even those that would be approved. Perhaps, with regard to products on the market, Husereau would try to address the concerns with subsidized production and dissemination of

knowledge, or with restrictions on manufacturer speech. Such interventions would have the considerable merit, relative to pre-market approval, of addressing directly the problem at hand.

* * * * *

When asked question 11b—“*Say the policy that requires pre-market approval was eliminated and, in its place, a policy was implemented allowing new pharmaceuticals/devices and initially classifying them as requiring a doctor’s prescription (pending a review process to consider dropping the prescription requirement). Do you think such a liberalized system would be superior to the current system?*”—Husereau says No, and then, in response to the followup “*Why not?*”, says:

Because good health care decisions require a more thoughtful approach that is less susceptible to cognitive biases based on incomplete data[.]

Consumers and doctors make myriad health-care decisions under the status quo, that is, with pre-market approval in place. I wish the questionnaire had prompted Husereau to say whether he would support policies putting more of those decisions under the thumb of the FDA, e.g., whether he would support a prohibition on off-label prescribing. Cognitive biases are frightening, but why is pre-market approval in particular the right

method to deal with them? (See my critique of Pedro Pita Barros’s “patients overestimate benefits” rationale.)

Husereau’s description of regulator decisionmaking as “a more thoughtful approach” (more thoughtful than what?) calls to mind Boersma’s attempted distinction between the FDA’s “variety of expertise” and others’ “individualized judgment.” Husereau says the pre-market approval approach “is less susceptible to cognitive biases”; he provides no supporting citations here, but the three authors cited by Husereau for evidence of specific biases do speak to the question of whether experts and elite committees are susceptible to the biases. Baron, Beattie, and Hershey (1988) expressly stated that information bias may afflict organizations as well as individuals:

Several accounts have suggested that use of an information heuristic might contribute to the performance of medical tests that are expensive, dangerous, and unnecessary [...], and, in corporations and institutions, to the gathering of data that have little relevance to the decision at hand (Feldman & March, 1981). (Baron et al. 1988, 90)

Shafir says the decisions of committees may be affected by compatibility:

Consider, for example, the initial weeding out process conducted by selection committees. [...] And assume a pool of candidates all of whom

have their faults and their good qualities, but some of whom have more of both than others do. To the extent that committees [...], as well as regular voters, are strongly invested in eliminating the candidates whom they perceive as having significant faults (with less emphasis on what may be their good qualities), we are predicted to be left with the impoverished candidates, politicians, and judges—those who provide us with few reasons to oppose them. (Shafir 1993, 555)

On omission bias in medicine, Asch and his collaborators wrote that “Clinicians and public health officials *must learn to* recognize and circumvent these pitfalls in reasoning” (Asch et al. 1994, 122, my emphasis). Mark Spranca, Elisa Minsk, and Jonathan Baron (1991), referenced by Asch et al. (1994) for a wider exploration of omission bias, express doubt with regard to the claim made by several philosophers that the omission-commission distinction is morally relevant—doubt they base in part on the ground that “Philosophers are not immune to psychological biases” (Spranca et al. 1991, 78, citing Hare 1981).

In his response to question 16b—“*In addition to systematic error on the part of consumers/doctors and/or uncertainty per se, is there any other sense in which you believe imperfect information to be a source of the market failure that justifies the policy requiring pre-market approval? If so, please explain.*”—Husereau clarifies somewhat:

The question is not about the existence of imperfect information, but who is framing its imperfection. Pre-marketing regulation also requires that uncertainty be framed for the benefit of society, by demanding information that would not otherwise be available.

Husereau's concern here seems in large part to be acquisition and presentation of information, neither of which is the distinctive aspect of pre-market approval.

Fortunately, the questionnaire goes on to propose a relevant reform in question 22b, "*As compared to the current system, would you favor making approval of a new drug automatic upon completion of the safety and efficacy testing processes specified by the FDA, regardless of what those testing results turned out to be?*" Husereau says No,

Because information that indicates an unfavourable choice can be re-framed as favourable for consumers and physicians.

I find this very unconvincing. Essentially everything on offer in every marketplace *is* (to say nothing of "can be") framed by its seller as a favorable choice, but many goods end up losing out anyway—because of nonseller sources of information, competition, consumer skepticism, and so forth.

When asked (in question 27b) if "*impartiality or commitment to the public good are sources of the government's superior ability to assure safety and efficacy,*" Husereau

says Yes. The followup question is “*In what ways does the FDA’s impartiality or commitment to the public good render it superior to doctors and patients in judging safety and efficacy?*” Husereau says:

Commitment to a population-based perspective means commitment to population-based data. Consumer-oriented information will mean societal[ly] harmful technology can be marketed as good for individuals.

When combined with Husereau’s reaction to question 22b, here we have a form of the argument that I speculated might comport with Arrow’s responses: that consumers will fail to understand that extraordinary attention and extraordinary respect should be accorded to the FDA judgment. While question 22b does not specify that the post-reform FDA will publish an interpretation or judgment of the testing results, Husereau’s concern that “information” can be “re-framed” suggests that he expects the post-reform FDA would provide an initial interpretative frame that conveyed some sense of its judgment. As with Arrow, I think it is safe to presume that Husereau would reject Table 1’s Variant #2, where approval would be automatic on completion of testing and the FDA judgment would be delivered directly to consumers via product labeling.

Do consumers inappropriately disregard the FDA’s judgments? Survey data shows that the FDA is well recognized and is held in fairly high esteem by Americans (Carpenter 2010, 12-13 n.16), though high esteem may not be quite the same thing as a

tendency to be attentive and respectful of the FDA's judgment. Perhaps a reasonably close proxy for according respect to the FDA's judgment is whether consumers follow the strictures of 'mainstream' medicine. Many consumers do, under the status quo, purchase goods and services from the practitioners of so-called alternative medicine, much of which is essentially quackery. David Eisenberg and collaborators (1998) estimated that 42% of American adults used at least one "alternative" therapy during the previous year. I think it is reasonable to construe such findings as showing there is much disregard, inappropriate or not, for the FDA's judgments. But what should be done, if anything, about such disregard?

Assume for the moment there is a Product X that the FDA would have banned under pre-market approval, but that reform Variant #2 has been put in place so instead such a product is labeled to indicate that it does not have the FDA's approval. Such a product takes its place among many unapproved products and services to which one may affix one's hopes, many of which are legally marketed under the status quo, such as medical procedures and dietary supplements. Why should a doctor or patient have particular interest in Product X, as opposed to an approved product or some other unapproved substitute? Perhaps there is a concern that Product X, coming as it does from a pharmaceutical manufacturer, would be marketed heavily—but its marketing could be regulated directly (and furthermore, Product X could be subjected to prescription requirements). What is the attitude of someone who supports pre-market approval over Variant #2, with regard to these substitutes for approved drugs? Perhaps they would like

to see such substitutes banned, or perhaps not; unfortunately the K&B questionnaire does not expressly elicit consideration of that matter. I am inclined to expect that there is much support, among supporters of pre-market approval, for increased restriction of drug substitutes. A ready interpretation of support for such restrictions is opposition to quackery, or a desire to draw patients into the network of credible medical science. But what theory or evidence is there that product bans a good means of dealing with quackery, or of keeping patients in touch with credible medical practitioners? Findings such as Eisenberg et al. (1998) show that “alternative medicine” is very alive and well under pre-market approval, and it is not obvious that extending the scope of pre-market approval to encompass more goods and services will substantially diminish quackery.

Regarding “population-based data”: Sellers, competitors, and other voluntary suppliers of assurance certainly do and will use such data to support and criticize claims to safety and efficacy, though it is often difficult to generalize from groups studied in a trial to broader populations. But I believe that, like Boersma, Husereau inappropriately neglects the probability that information about a patient’s circumstances can be put to valuable use in conjunction with the knowledge derived from trial data. Geoffrey Venning (1982) studied anecdotal reports by doctors of adverse drug reactions, finding that most such reports were “clearly correct.” David Kent and Rodney Hayward (2007, 1209) speak of a “growing awareness that the results of randomized clinical trials might not apply in a straightforward way to individual patients, even those within the trial. ... [I]mportant differences between individuals in each treatment group...can dramatically

affect the likelihood of benefiting from or being harmed by a therapy.” Jerry Avorn (2004, 173-175) relates a situation in which a drug for septic shock, Activated Protein C, won a borderline approval; later, external researchers looking at data submitted to the FDA determined that the clinical trial results were *very* favorable for one identifiable subgroup (viz., the most severe cases) while being *unfavorable* for others. Avorn reports that this research was widely used as the basis for treatment decisions going forward. One question is: Why should such a drug have even been near to a permanent ban? Another: What similar cases before the FDA, involving a drug useful to some patients but not to others, have gone in the other direction? Avorn hopes that in the future less emphasis will be given to “yes/no regulatory decisions.”⁴⁰

In addition to knowledge about an individual patient’s circumstances, such as the severity of a patient’s condition, knowledge of a patient’s genome is also increasingly relevant. It is well known, and has long been known, that individual response to drug therapy is highly variable (Clark 1937; Lu 1998). Researchers’ current understanding of

⁴⁰ “The world of prescription drugs has many biochemical Volvos—reliable, useful, and safe enough to reduce the risk of harm to the user, even in an accident. Rarely, a product will appear that’s more like a pharmaceutical Pinto: inherently dangerous, likely to crash and burn even with normal use. But most drugs are more like midsize Chevrolets. They work reasonably well, and their safety has everything to do with how they are used. The same Chevy can be all utility and no risk when driven by the legendary little old lady schoolteacher, but turn into a hazardous killing machine in the hands of her drunken teenage grandson. The better we understand this, the more we will be able to get beyond simplistic YES/NO regulatory decisions, to focus on those vitally important border zones where drug, patient, doctor, and system interact. For most drugs, that’s where the real action is.” (Avorn 2004, 184-185)

the sources of that variation is limited, but increasing, and has already yielded some treatment success stories (Lin 2007).

Andrew Harper and Eric Topol (2012) have called for “genomically guided clinical trials,” noting that “individuals enrolled to randomized clinical trials may appear phenotypically similar and balanced between cases and controls, [but] they are profoundly heterogeneous at the molecular level.” Harper and Topol suggest that advance screening of trial participants be done to “reduce heterogeneity and enable testing of very specific biologically based hypotheses.” Why would this lead to an improvement? Harper and Topol explain:

The track record of randomized trials that incorporate clinical phenotypes is fraught, with very large trials that cost hundreds of millions of dollars at best demonstrating small relative benefit of a 15–20% relative reduction in a composite clinical endpoint. This very inefficient and expensive model for the conduct of clinical trials and drug development is untenable. The small magnitude of efficacy can be easily overridden by a low incidence of major side effects, making a positive impact for a drug all the less likely. (Harper and Topol 2012, 1121)

Harper and Topol are pointing out that, *sans* genomic screening of trial participants, a trial will be conducted on many for whom the treatment is not expected to work, and also that the number of persons for whom the treatment *is* expected to work—assuming we could identify the members of that subgroup *ex post*—will be too low for us to have a very high level of confidence in the results for that subgroup. But profound heterogeneity means that, even when a trial is run with screening, we will still have genetic variation across the participants, and some of that variation may be important. Outcomes may vary, but the confidence we have as to whether this outcome variance is meaningfully large may not be very high; it may only be moderate or somewhat high. What happens then?

Nick Freemantle (2001) argues that a given trial tends to speak definitively only with regard to one “primary” prospectively identified effect or outcome to be measured over the entire group represented by the patients tested. Data on other “secondary” effects, and on the primary outcome measured for the various subgroups of the patients tested, are difficult to interpret. Since trials are expensive and time-consuming, these other effects and subgroup results may never be rigorously confirmed—yet they may be the data that are most applicable in many situations:

An individual patient faced with a serious condition may only have one opportunity to benefit from a potentially helpful treatment. Whatever the statistical results, the subgroup or secondary outcome results could provide the best available estimate of treatment effects for individual

patients. Health policy decisions relate not just to the individual patient but to all patients in the future. These decisions require greater rigour because an incorrect decision will be hard to rectify. (Freemantle 2001, 990)

The question confronting Husereau is whether pharmaceutical choice should be cast into the realm of “health policy decisions” (made by the government) or left to “the individual patient” (and her doctor). Freemantle acknowledges openly that, when decisions are made on behalf of “all patients in the future,” information valuable to some patients must be disregarded; by contrast, Husereau seems to deny that there is any tradeoff, suggesting that unapproved drugs only could be “marketed” as good for individuals. But cases where knowledge of the patient’s circumstances or genome are important, as well as cases where rigorous confirmation of the existing evidence is not forthcoming, illustrate that the tradeoff is real.

At questionnaire’s end, Husereau offered these general comments:

The questionnaire is not impartial and had a feeling of being leading. It is possible that a person neither believes or disbelieves conceptually and the option was not offered. It seems to be based in an extreme naivety about the power of individuals to make decisions about technology with broad societal implications. The authors have not seemed to consider the

wealth of literature from science an[d] technology studies and scientific philosophy, including Hacking, Shapin, Shaffer, Gallison, Pickering, Graham and others.

Here Husereau suggests more directly that there is an important distinction between “individuals” and some other class of decisionmakers, but I mostly disagree; see again my reaction to Boersma, where I argued that one cannot assume that, because a decision emerges from an organizational setting, the decision is founded on a basis for judgment superior to that of some decision attributed to an individual. Boersma was wisely less pointed, though, acknowledging that individualized judgment “may not be inferior.” Husereau, by contrast, places such emphasis on this distinction that it falls apart almost immediately. All “decisions about technology with broad societal implications,” from the election of a President to the success of major pharmaceutical companies to the appointment of a regulator, flow out of myriad actions and choices commonly attributed to individuals. A wealth of literature in political philosophy makes clear how inescapable is “the power of individuals” to effect these decisions.⁴¹

⁴¹ “Shivering man must rely on his own resources to pull himself from and stay out of the Hobbesian ‘warre’” (Buchanan 1975, 130).

Randall P. Ellis

Boston University, Department of Economics, Professor

summoned as a member of the *Journal of Health Economics* editorial board

Ellis supports pre-market approval, but not strongly. Ellis sees sources of market failure in imperfect information, as well as one “Other” source:

Insurance removes the effectiveness of the market in distinguishing socially beneficial drugs from those that are not worth the cost or risk.

The FDA does not consider cost in its approval decisions, and insurance would seem to have little if anything to do with doctors’ and patients’ judgments regarding the health risk posed by a drug, so it is unclear to me how Ellis could argue that pre-market approval resolves the issues (e.g., moral hazard) arising from insured patients; see on this my response to Pedro Pita Barros. Further, an insurer’s decision about which drugs to cover is quite separable both from treatment decisions and drug approval policy.

Ellis believes patients systematically err when dealing with uncertainties:

Behavior economics and studies of risk aversion show that consumers have a hard time making intelligent decisions when confronted with

risky prospects or decisions over time. Cutler, Finkelstein and McGarry
AER 2008 is one good example.

David Cutler, Amy Finkelstein, and Kathleen McGarry (2008) examine the phenomenon of selection in insurance markets. Specifically, they seek an explanation for empirical evidence that some insurance markets exhibit advantageous selection, despite the prediction of the model by Michael Rothschild and Joseph Stiglitz (1976) that insurance markets should exhibit adverse selection. Cutler, Finkelstein, and McGarry consider whether the puzzle can be resolved by accounting for variance in individuals' tolerance for risk, for which they use proxy measurements such as smoking and seat-belt usage. Their data analysis supports that hypothesis: "preferences for insurance—and their impact on risk occurrence and insurance purchase—may help explain the different patterns of selection observed in different insurance markets" (2008, 161). It is a bit of a leap from there to "consumers have a hard time making intelligent decisions when confronted with risky prospects or decisions over time." Such decisions *are* surely difficult, but must the errors arising from that difficulty be systematic? Ellis does not say, and neither does he provide evidence that distant regulators can better make these decisions. The FDA approval process involves its own risk calculus, one that has been criticized in many studies (e.g., Peltzman 1973; Gieringer 1985).

Ellis also says doctors systematically err, but when asked "*In what ways does doctor erring manifest itself?*" he explains why doctors err but not how they err:

Doctors err in prescribing in the same way that the entire medical system does because of the effects of insurance. The costs of pharmaceuticals is largely irrelevant to their decisions, only whether there is a positive benefit. Direct to consumer advertising of pharmaceuticals is also not particularly informative.

Ellis then rejects the reform proposed in question 11b—“*allowing new pharmaceuticals/devices and initially classifying them as requiring a doctor’s prescription*”—“For the reasons previously mentioned. Too many suspect new drugs would be prescribed.” But the effects of insurance, consumer difficulties in weighing risk, and uninformative DTC advertising are the only reasons Ellis has given. He has not postulated any kind of systematic erring.

Question 16b asks, “*In addition to systematic error on the part of consumers/doctors and/or uncertainty per se, is there any other sense in which you believe imperfect information to be a source of the market failure that justifies the policy requiring pre-market approval? If so, please explain.*” Ellis responds, “Agency problems in getting doctors to have the correct incentives for treatment.” How is pre-market approval supposed to remedy whatever deficiency Ellis perceives in incentives?

Later, Ellis rejects the reform proposed in question 22b, “*making approval of a new drug automatic upon completion of the safety and efficacy testing processes specified by the FDA, regardless of what those testing results turned out to be.*” He says:

Consumers do not pay the full cost of the drugs they use. Insurers and the government do. Hence it is [] appropriate for the government to play a role in deciding what they are willing to pay for.

Third-party payers surely must set restrictions on what they will buy for their clients, but it is invalid to invoke good business practice on the part of health-care purchasers as a justification for FDA pre-market approval. The government can and does refuse to provide certain drugs to Medicare recipients without imposing a universal ban on those drugs. The *Medicare Prescription Drug Benefit Manual* informs beneficiaries (at Centers for Medicare & Medicaid Services 2010, Chapter 6 10.6) that reimbursement is restricted to

any use of a covered Part D drug which is approved under the Federal Food, Drug, and Cosmetic Act, or the use of which is supported by one or more citations included or approved for inclusion in any of the compendia described in section 1927(g)(1)(B)(i) of the Act. The compendia are:

- I. American Hospital Formulary Service Drug Information,
- II. DRUGDEX Information System, and
- III. United States Pharmacopeia-Drug Information (or its successor publications).

Through this provision, the U.S. government empowers those three nongovernmental organizations to determine which off-label prescriptions that Medicare is willing and unwilling to purchase.⁴²

Ellis was next asked question 29b, “*As compared to the current system, would you favor a reform so that pharmaceuticals approved by the FDA counterparts in Europe, Japan, Canada, or Australia were automatically approved for the United States?*” He says No:

If the US adopted this policy, then pharma companies would just try to get approval of a new drug in the country where the review policies were the most lax. I would approve of allowing other country’s information to accelerate or otherwise affect the US review process.

⁴² The federal government’s reliance on two of these compendia with regard to reimbursement for off-label prescriptions dates to the Omnibus Budget Reconciliation Act of 1990. Use of the third compendium, Thomson Reuters’s Drugdex, began in 1997. A critical account of Medicaid’s reliance on the Drugdex compendium is provided by Armstrong (2003).

Ellis may be right about companies applying to the agency that is most lax,⁴³ but that hardly undermines the argumentation behind the reform. The reform speaks of four agencies competing in permitting drugs—one must be the most lax. If Health Canada, say, is swiftest and most permissive, that does not imply that it must be excessively so.

Marc L. Berger

Eli Lilly and Company

summoned as a member of the *Value in Health* editorial advisory board

Berger strongly supports pre-market approval, citing only imperfect information as a market-failure source of justification for the policy. Berger says that consumers do systematically err when coping with health uncertainties. However, in Berger's response to question 8b—“*In what ways does consumer or patient erring manifest itself?*”—he does not specify any biases, only instances of cognitive limitation and ignorance:

⁴³ When the reason to go before an agency is to secure access to markets, one can readily think that a producer will gravitate to the lowest hurdle. Malani and Philipson (2012, 104) make such a point with regard to off-label prescribing: “A drug need only be approved for one use to be available for almost any use that doctors may pursue. This affects a drug company's decision about the specific use for which to seek approval from the FDA. A company will consider the use for which proving safety and efficacy is easiest as well as the use for which marketing is most important.” But, imagine competing agencies that certify, not permit, drugs—there it is more plausible to think a producer will seek out the best certification it thinks its drug can acquire. This comparison gives reason to think the certification in itself could carry a more precise implied estimate of drug quality than would the approval in itself.

Patients have difficulty putting risks and harms into appropriate context. Moreover, how they put them into context is shaped by how the data is presented (ex. relative risk, absolute risk, how risk is placed into context). Moreover, the public does not fully grasp that the risk benefit profile for any treatment is always conditional -- we will always be learning more that will revise this assessment as more experience is gained with a treatment. Sometimes we will learn of additional benefits. Sometimes we will learn of additional harms. The dynamic nature of this for medical treatments is greater than that for other consumer goods.

Berger's concerns about consumer ignorance might weigh against self-medication and in favor of patients working through trusted physicians—but pre-market approval gives decisionmaking power not to physicians but to the regulator. Nowhere does Berger mount an argument that the grounds are faulty on which consumers decide to consult and to trust physicians, and in response to question 9b Berger says that physicians do not systematically err when selecting and prescribing therapies. So one might expect that Berger would affirm and support the reform proposed in question 11b: *“Say the policy that requires pre-market approval was eliminated and, in its place, a policy was implemented allowing new pharmaceuticals/devices and initially classifying them as requiring a doctor’s prescription (pending a review process to consider dropping the*

prescription requirement). Do you think such a liberalized system would be superior to the current system?” But he says No:

The government has a legitimate role in ensuring that the information disseminated to physicians and patients is accurate and fair. The evidence for benefits and harms is incomplete at the time of product launch and is therefore open to interpretation. The FDA acts as the advocate for the public to ensure a balanced interpretation of the available information.

Berger seems to be saying that *because* and *when* evidence is “incomplete,” a single national interpretation must be settled once and for all. But evidence is never complete. So what is the argument that the openness of evidence to interpretation should be closed at the point when “product launch” would have occurred? Berger had noted earlier that “we will always be learning more that will revise this assessment as more experience is gained with a treatment,” and that “sometimes we will learn of additional benefits.” Authorized investigators *might* continue to study a drug that cannot be marketed, but it is very doubtful that we can expect to learn just as much about a drug during periods when it cannot be marketed as during periods when it can be marketed.⁴⁴

⁴⁴ The leprosy indication for thalidomide was discovered after its withdrawal from the market by a doctor in Israel who first used the drug out of desperation, then traveled to Venezuela, where the drug was still available, to conduct the first double-blind study (Brynner and Stephens 2001, 121-125).

Berger also does not explain why only the government can provide⁴⁵ a “balanced” interpretation, nor why competing interpretations need be overruled by a unitary national authority. Berger’s description of the regulator as “the advocate for the public” is an implicit ascription of very good outcomes to democratic governance, as if elections and political processes inevitably resolve myriad views, situations, and interests into wisdom. Not surprisingly, Berger later says he believes that uncertainty *per se* constitutes a market failure, adding “See my previous comments.”

Berger (in question 17b) rejects public-goods aspects of knowledge as a justification for pre-market approval, but (question 20b) thinks that pre-market approval does induce the generation of more knowledge than there would be in the absence of the policy. He is then asked question 22b, “*As compared to the current system, would you favor making approval of a new drug automatic upon completion of the safety and efficacy testing processes specified by the FDA, regardless of what those testing results turned out to be?*” Berger says No, and explains:

The government has a legitimate interest in the public health and safety.

If a new product is less effective and is associated with more harms than

⁴⁵ Berger says “ensure,” not “provide,” but in the context of pre-market approval the imposed interpretation is that of the regulator. The FDA does not just “ensure” that physicians’ and consumers’ interpretations are “balanced.”

available treatments, the government appropriately should not allow it to be marketed.

Here Berger effectively sets out a model of pre-market approval in which each pharmaceutical has been definitively associated by the FDA with a particular indication, with some level of effectiveness, and with some count of “harms.” Berger then imagines that the regulator compares each new drug to this supposed definitive set of “available treatments,” banning those new drugs that fail to outstrip any existing competitor on either effectiveness or safety.⁴⁶

All models are simplifications, but some are more robust to the weakening of assumptions than are others. To an economist, the most outstanding of Berger’s assumptions might be the absence of price or opportunity cost from the model. It is generally true that the FDA does not take cost into account when making approval decisions, but realize that the FDA also does not typically require new drug performance to match or surpass that of competing treatments.⁴⁷ If the FDA did require new drugs to outstrip some existing competitor on safety or effectiveness, but still did not consider costs, then consumers would miss out on the gains to be had from a new drug that was

⁴⁶ A formal model similar to Berger’s is provided by Zweifel, Breyer, and Kifmann (2009, 403-404).

⁴⁷ The FD&C Act specifies that, for approval purposes, a drug’s effectiveness is in evidence merely when “it could fairly and responsibly be concluded by...experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof” (21 USC 355(d); see also, e.g., Gagne and Choudhry 2011).

less expensive than existing competitors and superior to placebo, but slightly inferior to existing competitors on safety or effectiveness.

Neither is Berger's model particularly robust to basic difficulties in drug evaluation. Imagine a model in which each drug can be measured not on Berger's two aggregated dimensions of "effectiveness" and "harms," but rather on N dimensions of the sort that researchers actually confront: effect on mortality; magnitude and duration of changes in felt pain, tumor volume, mobility, strength, energy level, sleep, digestion, appetite, mood, capacity for pleasure, appearance, etc.; potential for complications such as tissue loss, bleeding, allergic reaction, or adverse interaction with other drugs A, B, C...; quickest onset; easiest administration; and so forth. Would Berger hold that a new treatment better than at least one existing treatment on at least one dimension should be allowed to enter the marketplace? That is the standard he seems to set for a space defined by two aggregated dimensions of safety and effectiveness,⁴⁸ but applying it in this N -dimensional space would create such a low bar to clear that it's hard to see why we'd bother with pre-market approval at all.

Finally, Berger's model assumes that a sufficient accounting of effectiveness and harms can be acquired by the government prior to the entrance of a drug into the messy

⁴⁸ FDA reviewers do not apply Berger's seeming standard, and neither of course do they have direct access to uncontroversially aggregated measures of safety and efficacy. Instead there is continuous debate (e.g., Lauer and Topol 2003) over how multiple dimensions of drug effectiveness (often formalized as "end points" in the context of a clinical trial) should be resolved or factored into approval and treatment decisions.

real world. But there are sharp limits on what can be learned from clinical trials. Patients in trials are often relatively healthy and are not taking multiple drugs for various simultaneous indications, while the elderly and the very sick tend to be underrepresented (Collet 2000; Avorn 2007); also, any populations that come to use the drug off-label for other indications will systematically differ from those who participated in the clinical trials for the approved indication (David et al. 2010, 2). Trials are brief in duration, and thus provide limited information about drugs designed to be taken over long periods or the effects of which (e.g., on mortality) cannot be judged quickly (Satia-Abouta et al. 2003; Avorn 2007; Budish et al. 2013). Much valuable information can only be surfaced by widespread use of the drug, particularly safety information (Lasser et al. 2002; Avorn 2004, 106-114) but also with regard to serendipitous discovery of new indications for the drug (Tabarrok 2000). Furthermore, once a drug and associated testing information are ‘out,’ researchers other than those affiliated with the sponsor company and the FDA may take an interest in examining the drug’s effectiveness or safety profile and—holding different predispositions and preferring different methods—may generate new data or offer competing interpretations of the existing data (McGarity and Shapiro 1980, 840-844; Gale 2009).⁴⁹

⁴⁹ Krumholz et al. (2007, 122) suggest that “independent investigators,” given the data submitted to FDA by Merck on behalf of Vioxx, could have surfaced earlier the high cardiovascular risk that led to that drug’s withdrawal five years after approval.

Another reform rejected by Berger is that proposed in question 29b, “*that pharmaceuticals approved by the FDA counterparts in Europe, Japan, Canada, or Australia were automatically approved for the United States.*” His reason:

Since we will always be dealing with uncertainty, then the values of different societies will impact approval decisions -- that is, different countries may draw different conclusions about what is an appropriate risk-benefit profile. What is also an acceptable profile depends on the context in which a new drug will be used. Treatment patterns differ significantly across countries. Therefore the context for approval differs.

“Treatment patterns” also “differ significantly across” states, cities, medical practices, and individual conditions, and across time, but Berger finds it appropriate only that “different *countries* may draw different conclusions.” The reasons that Berger raises here in fact militate for individuated, decentralized decisionmaking by the parties with the local knowledge and intent to take such differences and details into account—exactly what would be advanced by the reform proposals that Berger rejected throughout the questionnaire.

In response to question 32b, “*Do you believe the pre-1962 historical record shows systematic failure in assuring efficacy?*”, Berger answered Yes. He explained:

This was a forced choice question. Yes or no. I'm not thoroughly familiar with what happened before 1962. For one thing, there were a lot fewer prescription drugs on the market. The Thalidomide story was an important stimulus for more stringent requirements regarding testing prior to approval.

The thalidomide disaster, beyond its historical importance, can and should be mined for lessons about the risks of new drugs, but Berger does not do so here.

John E. Brazier

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summoned as a member of the *Applied Health Economics and Health Policy* editorial board

Brazier strongly supports pre-market approval. In the closed-end question 5b, he selects "Imperfect information" and "Public-goods aspects of knowledge" as sources of market failure justifying pre-market approval, and he also describes an "Other" source:

FDA is to my (British) is not Government per se, but Scienti[fi]cally informed agency charged with making decisions in the public interest. In this regard I think they are better than a general public who are at the mercy of well financed advertising campaigns. Establishing that a drug is effective and safe is not some[th]ing most of us can do in our spare time.

Brazier seems to say that the FDA is not “Government per se” because from his (British) perspective on the FDA, the FDA should not be considered part of the U.S. government. He describes the FDA as being an “agency charged with making decisions in the public interest,” as if this were part of an explanation as to why he does not consider the FDA to be part of any government. Perhaps Brazier means to distinguish between “making decisions” (nongovernmental?) and enforcement thereof (government), but that distinction would write Congress out of the U.S. government as well, which is absurd. Or perhaps he means to distinguish between ‘scientifically informed agencies’ (nongovernmental?) and whatever he would call the rest (government), but this would be that much stranger—as if scientists hired by the government somehow remain outside of it. The plain fact is that the FDA is an operating division⁵⁰ of the Department of Health and Human Services, “the United States government’s principal agency for protecting the health of all Americans and providing essential human services.”⁵¹ As Carpenter (2010)

⁵⁰ <http://www.hhs.gov/open/contacts/index.html>

⁵¹ <http://www.hhs.gov/about/index.html>

makes impressively clear, the FDA wields powers uniquely governmental, giving as it does permission to engage in peaceful acts otherwise banned by government. Brazier would seem either to be working from an unusual definition of *government* or to be exhibiting a form of the denial, associated above with Cornelis Boersma, that pre-market approval is a coercive policy.

Brazier's remark about "well financed advertising campaigns" seems to imply that, without pre-market approval, drugmakers would find it profitable to finance the promotion of unworthy drugs. But an irresponsible advertising strategy may prompt reactions by patients and doctors that reduce its profitability. The model put forward by Benjamin Klein and Keith Leffler (1981), which its builders illustrate with an example from the market for children's aspirin (*ibid.*, 632 n.18), suggests that expensive advertising campaigns tend to be valid signals of product quality.⁵² Brazier also does not explain why his worry that consumers' "spare time" is insufficient to assess drug quality is better addressed by pre-market approval than it would be by, say, the public purchase of some pharmaceutical experts' full attentions to assess drug quality.

⁵² "This analysis of advertising implies that consumers necessarily receive something when they pay a higher price for an advertised brand. An expensive name brand aspirin, for example, is likely to be better than unadvertised aspirin because it is expensive. The advertising of the name brand product indicates the presence of a current and future price premium. This premium on future sales is the firm's brand name capital which will be lost if the firm supplies lower than anticipated quality. Therefore, firms selling more highly advertised, higher priced products will necessarily take more precautions in production" (Klein and Leffler 1981, 632).

Brazier says Yes when asked whether patients systematically err when coping with uncertainties related to health and treatment, but he qualifies the answer:

This is a strange question, because I am not sure what is intended by the term systematic. The problem consumers face is how to make the right decisions, when their very life may depend on getting it right - in the face of often extremely complex evidence.

By “systematic error,” scientists refer to measurement error that is not random. Random error, by definition, is unpredictable and may impact any measurement. In the present context, we merely mean to find where consumers are going wrong—again, like a steering column that pulls to the right—that might be correctable by intervention.

Brazier raises the daunting spectre of a life-or-death decision. That a decision is merely important, is hardly an argument that it be placed in the hands of a government expert; one’s life is more important to oneself than it is to the expert. I see decision importance as being operational primarily with regard to incentives and motivation; whatever the advantages of the expert, they would seem not to lie in these areas. One whose “very life” depends on a decision will be more motivated than most all others to identify and listen to those who are especially good at obtaining product information or at rendering valuable interpretations. By comparison, the FDA and its Congressional

sponsors may be less motivated to find, and possibly defer to, those with superior expertise.⁵³

Regarding “extremely complex evidence,” complexity suffuses the medical marketplace, confronting both consumer and expert. Relevant here are my comments regarding consumers’ use of expert analysis of clinical trial data, made above in response to Cornelis Boersma.

Brazier continues, regarding patient erring:

There might be a tendency for consumers to believe a new treatment is better, when indeed it may not be and actually do them more harm than good compared to the alternatives.

Is there such a tendency? Brazier won’t go so far as to say there is, nor to provide evidence for one. If patients excessively favor new drugs *because* they are new, this might justify an intervention that improves knowledge about or restricts those drugs that are *newer*, but pre-market approval bans drugs that the regulator has not rated highly in

⁵³ "The FDA isn't obstructing progress because its employees are mean-spirited or foolish. But for decades, Congress has starved the agency of critical funding, limiting its scientists' ability to keep up with peers in private industry and academia. [...] The FDA can convene advisory committees of outside experts, but these experts weigh in only at the end of the regulatory process. Worse, congressionally mandated conflict-of-interest rules keep many of the most knowledgeable academic and industry scientists off advisory committees out of fear that industry ties might bias their judgment" (Eschenbach 2012).

an assessment of *quality*. If excessive favor for new drugs can be traced to other reasons, e.g., because information is thin or because interpretations vary to a great extent, then the implication is that patients use better judgment with regard to older drugs because those other reasons have waned in relevance, perhaps because of learning over time.⁵⁴ Certainly we would not want a pre-market approval scheme that bans particularly those drugs about which learning takes place over longer time horizons; perhaps better interventions could merely facilitate the learning process.

Brazier's final sentence about patient erring is:

Furthermore, [consumers] are usually spending the health care dollars of an insurance company or the public purse, and so this waste also has an impact on others.

What is "this" waste, and is there a relationship between such waste and the pre-market approval policy? Again, governments can and do come up with lists of products they are unwilling to purchase without going so far as to impose a general ban on the products; see my response to Randall Ellis.

When asked if doctors err systematically, Brazier says Yes:

⁵⁴ Public Citizen's Health Research Group advises consumers not to use non-"breakthrough" drugs until seven years after FDA approval (Wolfe 2012).

Again, I do not like the term of systematic. As before, there are arguments about understanding complex scientific data and the impact on others.

The point that physicians may not be able to analyze the data for themselves works only in favor of facilitation of expert analysis, not in favor of overriding physicians' judgments—which could be based on expert analysis, along with situational knowledge, costs, etc.—with the FDA's judgments.

When asked (in question 11b) for the first time to evaluate a potential reform—*Say the policy that requires pre-market approval was eliminated and, in its place, a policy was implemented allowing new pharmaceuticals/devices and initially classifying them as requiring a doctor's prescription (pending a review process to consider dropping the prescription requirement). Do you think such a liberalized system would be superior to the current system?*—Brazier rejects the proposal and again falls back on his “previous arguments about lack of information, uncertainty and externalities.” To my mind, as Brazier failed earlier to identify systematic doctor erring, he likewise fails to give any clear argument for rejecting this proposal.

In addition to patient and doctor erring, Brazier says he sees more senses in which imperfect information is a source of market failure justifying pre-market approval:

I would add lack of information and assessment of the quality of evidence. A key role of FDA and similar agencies around the world is to provide an independent and scientifically informed review of the evidence. So it is about understanding 1) what is the likely mean effect and 2) what is the uncertainty around this. These both require someone able to understand the evidence that was collected and how it was analysed. The other issues concerns that fact that most health care is funded by a third party who need to be assured that the scientific evidence has been properly assessed. Not something most consumers, physicians or even economists are in a position to do. However, also[] believe that consumers and producers should be involved in the process, particularly where there are important trade-offs to be made between different outcomes of treatment.

These arguments seem little different than what Brazier offered earlier, with the addition of the notion that the FDA is “independent” (criticized above in my remarks on Cornelis Boersma’s responses).

Brazier is then asked question 18b: *You indicated that public-goods aspects of knowledge are a source of the market failure that justifies the policy requiring pre-market approval. Do you think that this source of market failure would be better*

addressed with a policy that subsidizes the generation of knowledge, e.g., via the National Institutes for Health? He says No:

There needs to be some kind of overall collation of evidence and clear guidance. Who is going to be able to read the NIH report and match this up with advertising from drug companies and really make sense of the value of the new product?

Brazier responds as if he is rejecting the reform because there are public-goods aspects of “collation of evidence” and “guidance.” It should be clear that the NIH would provide “collation of evidence” when it issues a “report.” I think just as clearly there is an invitation here for Brazier to discuss the possibility of the NIH (or FDA) providing guidance without banning products, but he declines that invitation. Brazier’s talk of “overall” collation, “clear” guidance, and “really” evaluating products is not dissimilar to Marc Berger’s assertion that one “balanced interpretation of the available information” should be enforced upon everyone, but Brazier’s questioning “who?” more plainly seems to derive from the sort of “unexamined precept that there must be some kind of parent out there, a yearning for some kind of validator” that Daniel Klein (2008, 333) sees as pervading discourse around the FDA.

Brazier goes on to reject a reform (proposed in question 22b) automatically approving drugs that complete an FDA testing process; asked “Why not?” he writes

“Ditto previous arguments.” Brazier does favor a reform making U.S. approval automatic for drugs approved by FDA counterparts in other countries.

Anthony John Culyer

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summoned as a member of the *Journal of Health Economics* editorial board

Culyer strongly supports pre-market approval. In addition to imperfect information rationales, in question 6b he lists several “Other” sources of justification for the policy:

Commercial pressures for too-early marketing (e.g. thalidomide);
complexity of appropriate decisions about prescribing; misleading
marketing; contradictory clinical guidelines; direct to consumer
advertising; weak and variable agency relationships,...

“Commercial pressures for too-early marketing” might be interpreted as suggesting there is excessive demand for newer products, a possible bias addressed above in my response to John Brazier. “Complexity of appropriate decisions about prescribing” also seems to

echo Brazier. “Misleading marketing” and “direct to consumer advertising” already are regulated directly. “Contradictory clinical guidelines,” in the context of pre-market approval, sounds similar to the calls by Brazier and Marc Berger for a single national interpretation to be enforced. I hesitate to interpret “weak and variable agency relationships”—do we desire strong and invariable agency relationships? If so, does pre-market approval bring them about? Consider my response to Kenneth Arrow regarding disinterestedness.

Culyer says No when asked if either consumers or doctors err systematically in selecting treatments, but then, in rejecting the reform proposed in question 11b (*“allowing new pharmaceuticals/devices and initially classifying them as requiring a doctor’s prescription”*) he says:

Most doctors not qualified to evaluate evidence of efficacy or risk of harm. most doctors have irrational attitudes to risk. I prefer evidence-informed prescribing.

Doctors being “not qualified to evaluate evidence” is similar to Brazier’s concern about complexity. As I pointed out in response to Cornelis Boersma, the division of knowledge is not a market failure. A doctor needs not be specialized both as clinician and researcher in order to make appropriate decisions as to which pharmaceutical experts to trust and how to weigh their advice.

In my understanding of the language, doctors possessed of “irrational attitudes to risk” indeed would make systematic errors. But Culyer does nothing to explain why pre-market approval is a good policy response to the disturbing situation in which physicians’ treatment decisions would not be “evidence-informed.” The failure of doctors to practice “evidence-informed” medicine would be a wide-ranging problem only vaguely and very incompletely addressed by placing a ban on certain products.

Culyer is then asked “*If neither consumers nor doctors err systematically in these matters and uncertainty per se does not constitute a market failure, then in what sense do you believe that imperfect information is a source of the market failure that justifies the policy requiring pre-market approval?*” He responds:

There can be lots of error without it being systematic or tending in a singular direction. Plain ignorance, which in some liberal worlds would be rampant, is likely to do indiscriminant harm as well as occasional good.

An arguably not-so-liberal policy aimed at reducing “plain ignorance” might be to subsidize the production of knowledge. However, the distinctiveness of pre-market approval lies in product bans, not in knowledge production. Bans might be a means of curtailing damage caused by “rampant” ignorance, but bans are not a means of reducing

ignorance. Culyer's talk of "some liberal worlds" may be a poke at the makers of the questionnaire, which he later describes as "biased," but overall his response seems not to engage the question as it pertains to pre-market approval.

Culyer says public-goods aspects of knowledge do not justify pre-market approval, but says Yes when asked (in question 20b) whether "*pre-market approval induces the generation of more knowledge about the new pharmaceutical than there would have been in the absence of the policy.*" He then rejects the reform proposed in question 22b, "*making approval of a new drug automatic upon completion of the safety and efficacy testing processes specified by the FDA, regardless of what those testing results turned out to be.*" When asked "Why not [enact the reform]?" he says:

Many rational insurers (like mine) would want evidence of cost-effectiveness in order to offer competitive premiums for insurance against evidence-informed prescriptions.

First of all, a mere wrinkle to the proposal—that FDA decide whether to give a certification or seal of approval to each new drug, as in Table 1's Variant #1 above—would address Culyer's concern, or address it at least as well as does the status-quo regime (again, the FDA prides itself on not considering costs in approval decisions). As the reform proposal stands in the question, insurers and other decisionmakers would *have* to judge, or rely on the judgments of others, as to whether a product is worth using. Does

Culyer mean to argue that non-FDA entities cannot make evidence-based judgments? If so, this would be among the strongest possible statements of FDA specialness, one that cries out for explanation. But Culyer did not select (in question 5b3), as a source of market failure justifying pre-market approval, the idea that “*Government has superior ability to assure safety and efficacy,*” nor does he talk anywhere else about what might make the FDA special.

The next question asks whether Culyer would “*favor a reform so that pharmaceuticals approved by the FDA counterparts in Europe, Japan, Canada, or Australia were automatically approved for the United States.*” He says No:

Generalization from one jurisdiction/culture/etc. is hazardous. That’s not to say there could not be useful learning.

Whatever it may be that makes the permitting of a drug wise in one culture (or “jurisdiction”), but not in another, could also apply across cultures within a country. It would be remarkable if all the cultural differences relevant to hazard in pharmaceutical permissiveness were demarcated by political borderlines. And yet Culyer strongly advocates the uniform imposition of pre-market approval across the United States, while balking at partial policy union with Canada.

Culyer's responses seem most appropriately interpreted by incorporating the assumption that he views the actions of national governments are guided by all-but-unique access to truths. The notion that the regulator knows, and knows best, seems so certain as not to be worthy of any remark, to the point where Culyer finds the K&B questions incomprehensible or unwarranted (they are "too framed"). It would seem that for Culyer "weak and variable agency relationships" exist among manufacturers, doctors, and patients, but nowhere the regulator is involved, so "lots of error" naturally justifies intervention by a superior entity.

F. M. Scherer

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summoned as an economist writing on the FDA cited in Klein (2008)

Scherer is a strong supporter of pre-market approval. He finds market failure rationales for the policy in imperfect information, public-goods aspects of knowledge, and another source he describes as follows: "It has alas been historical fact that, despite the threat of significant tort liability for harmful drugs and devices, manufacturers have been less than diligent in ensuring that pre-market testing is adequate and that public health hazards are avoided." Such hazards cannot be "avoided" entirely, and they continue to crop up under the current policy regime, as with Vioxx. There might be more

‘bad drugs’ introduced on a liberalized market, but that could be redeemed by other benefits. A lack of manufacturer diligence could, perhaps, be countered in a liberalized environment by consumer skepticism and the revoicing of demand for assurance of safety and efficacy from the political to the market sphere.⁵⁵

Scherer says consumers systematically err when coping with health uncertainties:

Most consumers lack the information needed to evaluate the drugs they take; indeed, many don’t even read the FDA-required label indications. It has also been my experience, marked to be sure by some pleasant exceptions, that drug prescribers are so harried that they do not consider seriously all relevant safety and efficacy effects. I personally have had ulcers from ill-prescribed drugs and was once prescribed drug therapy for what turned out to be a serious cancer. I once attended a University of Chicago seminar at which a physician described the exquisite care he applied in choosing drugs for his patients. I sat there thinking, My God! Where do I find such a physician?

⁵⁵ David Dranove, a respondent to the K&B questionnaire and a mild opponent of pre-market approval, rejected the reform making approval of a drug automatic upon completion of the FDA testing processes, explaining in part: “Perhaps this is a short term concern, but the FDA testing process is viewed as an imprimatur of quality.” I interpret Dranove as suggesting that institutional reform will work best if doctors and consumers are first robustly alerted to the fact that they need to be giving form to their demand for assurance of safety and efficacy through market activity—by looking for seals of approval, by patronizing only reputable manufacturers and retailers, etc.—rather than through the bureaucratic or political process.

Scherer's remarks remind me of Kenneth Arrow's talk of consumers not having "the full information." That consumers don't have some information that would be useful, does not make their erring systematic. Possibly Scherer is suggesting that a failure to read the label (for example) is a behavioral error, that a consumer who doesn't read a label is likely placing too much trust in the guidance of her physician, pharmacist, manufacturer, or retailer. If so, what is the evidence that trust is misplaced?

In response to question 9b, "*Do you believe that doctors systematically err when selecting and prescribing therapies?*", Scherer selected the "No" option. He then said the liberalization proposal of question 11b, "*allowing new pharmaceuticals/devices and initially classifying them as requiring a doctor's prescription (pending a review process to consider dropping the prescription requirement),*" would not be superior to the current system. Asked "*Why not?*" he wrote:

Your earlier question asked whether physicians systematically err; I replied no. But they do err randomly, and frequently, in large measure because they are simply so busy that they don't have time to consider indications and contra-indications. Also, there are informational economies of scale in having an agency like the FDA consider in detail, however imperfectly, all the evidence available on indications and contra-indications. Most physicians simply don't have time to do this.

Like consumers, physicians need not be expert in analyzing clinical trials, only in locating trusted experts, as I have pointed out in response to John Brazier and Anthony Culyer. Furthermore, as noted in my response to Arrow, the FDA could provide its “safe and effective” judgment in one ‘bit’ of information, via mere certification rather than banning. We rely on physicians, who are indeed given much information, to choose appropriately from among the universe of approved drugs. Adding some more drugs to that universe, plus the one ‘bit’ of information indicating the FDA’s certification, seems a straw unlikely to break physicians’ backs.

Scherer’s concern about “informational economies of scale” is difficult to understand. I tentatively interpret Scherer to be saying that the good to which such economies apply is analysis: “consider[ation] in detail...[of] all the evidence available.” What reason is there to believe that, the larger the organization, the higher the quality of its analyses? Analysis attributed to very large organizations can be politicized, clouded by groupthink, or otherwise errant; see on this my response to Cornelis Boersma regarding a distinction between “individualized” judgment and judgments commonly attributed to groups. Further, there seems no reason to think that an information-analysis organization needs be vastly larger than the size of the information-collection organizations discussed in my response to Kenneth Arrow. And how does this justify pre-market approval? The obvious, direct remedy is a subsidy of knowledge production.

Conveniently enough, Scherer then encountered question 18b: “*You indicated that public-goods aspects of knowledge are a source of the market failure that justifies the policy requiring pre-market approval. Do you think that this source of market failure would be better addressed with a policy that subsidizes the generation of knowledge, e.g., via the National Institutes for Health?*” Scherer opts for No, then writes:

The question was, better addressed, implying that NIH would substitute for what FDA does, as [Marcia] Angell has suggested. NIH makes wonderful contributions to the generation of health care knowledge. But to add the kinds of responsibilities FDA now carries would not exploit its comparative advantage and indeed might even for bureaucratic reasons be less than advantageous than having an agency whose principal mission is ensuring safety and efficacy.

Whether the NIH is the correct institution is not central to the question as posed. If market failure *is* better addressed by the generation of knowledge than by pre-market approval, and if “for bureaucratic reasons” a new agency needs be formed from the ground up to handle the generation of knowledge about new drugs, probably the costs to taxpayers of starting such a new agency would be dwarfed by the far-reaching gains from undertaking this appropriate liberalization.

Scherer rejects the reform that would make drug approval “*automatic upon completion of the safety and efficacy testing processes specified by the FDA, regardless of what those testing results turned out to be.*” He gives this reasoning:

The historical record is clear: FDA has made serious errors, and physicians have in large numbers prescribed the approved drugs. So the system is imperfect. But without the informational function the FDA performs, there would be even more prescribing errors.

Scherer’s worry about a world “without the informational function the FDA performs” is misplaced, given that the proposed reform is specifically designed to leave that very function in place. If Scherer means to say that the fact of approval itself is “informational,” then his concern (like Culyer’s) can be addressed by adding to the reform the mere wrinkle that FDA issue seals of quality approval. As in response to question 18b where Scherer fixated on the parenthetical example of the NIH, here again I do not see Scherer stepping up to address the issue at hand. Like Boersma, Scherer evinces denial about the fact that pre-market approval is a sweeping legal prohibition on voluntary activity; he supports it, yes, and yet he evades the repeated opportunities really to justify that position.

Scherer also does not favor the reform to automatically approve drugs that are granted market access by FDA counterparts in Europe, Japan, Canada, or Australia.

Though he sees value in having a competitive environment, he sees the status quo as close to optimal because of the “informational economies of scale”:

Well, we in the United States are big guys (to be sure, like the Europeans), better able to exploit the informational economies of scale. And given the inevitability of agency error, it’s good to have several responsible regulatory agencies around the world, so that errors by one may be corrected by others’ correct findings. The same logic applies for decentralizing regulatory functions to the individual states, but in this case, the informational economies of scale call for more centralization. Creation of a central European drug approval agency reflected that tradeoff.

John Hutton

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summoned as a member of the *Health Economics* editorial board

Hutton supports pre-market approval, but not strongly. He says patients systematically err in dealing with health uncertainties:

I am basing this on personal and professional experience rather than evidence. Some patients tend to underestimate or ignore uncertainties when relying on doctors to make decisions for them. The current system of drug prescription leaves consumers less chance to make errors in choice of treatment. Evidence on adherence to treatment indicates that some patients may not understand the implications of treatment or that doctors may not be correctly interpreting the needs of their patients

Hutton's claim that patients "underestimate or ignore uncertainties when relying on doctors to make decisions for them" hardly seems to support the notion that patients should be made to rely on the FDA to make decisions for them. Further, in the same way that prescription requirements may leave consumers "less chance to make errors in choice of treatment," so would, say, a ban on all drugs. The complex of decisions and results brought about by such requirements (or such a ban) may still be inferior to that which would prevail in their absence. Whatever it is that "patients may not understand" or that "doctors may not be correctly interpreting," Hutton would need to argue for the regulator's superiority, rooted in some sort of distinctiveness about the regulator, in order for such points to bolster a case for pre-market approval.

Hutton says doctors systematically err when prescribing therapies:

Individual doctors do not have the time or expertise to appraise the evidence on each individual product they might prescribe but many do not follow evidence-based guidelines.

Doctors need not evaluate the evidence themselves, but need only identify experts who are trustworthy; see my responses to Cornelis Boersma on doctors' profit motive and on valuation of existing evidence. Hutton's complaint about doctors not following "evidence-based guidelines" is similar to comments above by Anthony Culyer, and as above I would ask why banning some drugs—as opposed to, say, publicizing the failure of doctors to follow evidence-based guidelines—is an appropriate regulatory response.

Hutton rejects the reform proposed in question 11b, "*allowing new pharmaceuticals/devices and initially classifying them as requiring a doctor's prescription (pending a review process to consider dropping the prescription requirement).*" When asked why he does not think the reformed system would be superior to the status quo, he poses a series of questions:

Would doctors be willing to prescribe in such circumstances? How would they be informed of the characteristics of new treatments? Who would validate the claims of manufacturers? Is the proposal that companies should continue to undertake clinical trials, but no formal assessment of them would take place? This would not speed market

access very much. How would the review process to convert products to O[TC] differ from the current one?

The frequency of off-label prescribing, not to mention the pre-FDA historical record, strongly suggests doctors would continue to use drugs after a repeal of pre-market approval policy. But realize also that each prescription is a choice of a particular drug, not merely a choice generally to use drugs. Doctors regularly confront an ocean of approved therapies from which to choose, and FDA approval plays only a limited role in their decisions alongside influences such as: third-party certification, hospital formularies, advice from peer physicians, assurance from manufacturers, and their own experience and training.

Hutton's "who would validate" language seems as derivative from Daniel Klein's "unexamined precept" (Klein 2008, 333) as was John Brazier's language. Further, when Hutton wonders whether "no formal assessment...would take place" in a reformed system, it is hard to see what meaning Hutton could be ascribing to *formal* beyond merely 'by the government.' We should value an "assessment" because it is accurate or appropriate, not because it is formal or governmental—yet Hutton did not choose "*Government has superior ability to assure safety and efficacy*" as a source of market failure (and here Hutton is again similar to Anthony Culyer).

In addition to systematic erring by doctors and patients, Hutton describes another sense in which imperfect information justifies pre-market approval:

Pre-market approval influences the type of information produced by manufacturers. Without it the information needs of informed consumers would be less likely to be met. The way the information is used by the FDA and its peers in other jurisdictions is not always ideal, but that can be changed without removing the requirement to produce the information. In its absence markets for information would no doubt develop. Supplying them would impose costs on manufacturers and health care providers. A priori it is not clear that this would be more efficient.

Nor is it clear a priori that the current regime is more efficient. Hutton here is placing a presumption for the status quo before Smith's presumption against government intervention, as if the economists' discourse around appropriate government policy was built on identifying 'status quo failures' rather than 'market failures.'

By noting that "The way the information is used...can be changed without removing the requirement to produce the information," Hutton anticipated question 22b: *"As compared to the current system, would you favor making approval of a new drug*

automatic upon completion of the safety and efficacy testing processes specified by the FDA, regardless of what those testing results turned out to be?” Hutton replied No:

This would place information in the public domain. However, such a system would rely on the ability of clinicians (and patients) to determine whether and for whom the treatment would be benefic[i]al. Many aspects of this are generalisable, and probably best done in a coordinated rather than a decentralis[e]d way. Major health care payers and providers could carry out their own assessments. The end-user would most likely be confronted with a range of information sources with varying degrees of independence. Creating flexibility in FDA decision-making, for example, with more conditional licensing, would be preferable.

It is notable that Hutton opposes *coordinated* to *decentralized*. Must a decentralized system be discoordinated by its nature, or a centralized system coordinated? If so, perhaps the sort of coordination Hutton describes is not particularly valuable.⁵⁶

⁵⁶ Klein (2012b, 35-77) distinguishes two senses of coordination, which he terms *mutual* and *concatenate*. Klein shows that usage of *coordination* in the mutual sense is currently dominant in economic discourse, particularly in applications of game theory, while the concatenate sense dominated in earlier times. Talk of mutual coordination may carry little normative or welfare impact, e.g., it is possible to be mutually coordinated with others in the generation of outcomes that are very suboptimal for all parties. Meanwhile, to describe some patchwork of activity as being coordinated in the concatenate sense is, in large part, to judge it favorably. Centralization certainly seems

Just as Hutton’s post-reform “end-user” is “confronted with a range of information sources with varying degrees of independence,” so is the contemporary FDA (as is, in fact, the contemporary “end-user”). The operative question is why the FDA’s judgment with regard to that information should be made to trump all others’ judgments. Hutton may be correct that “many aspects of [determining whether and for whom a treatment would be beneficial] are generalisable,” but Hutton does not explain why the non-generalizable aspects, e.g., those related to local knowledge possessed by patient and physician, should be disregarded entirely; see on this my response to Don Husereau on “population-based data.”

Hutton also rejects the reform proposed in question 29b, “*that pharmaceuticals approved by the FDA counterparts in Europe, Japan, Canada, or Australia [be] automatically approved for the United States.*” He says:

Some degree of harmonisation of decisions would be efficient. It could be extended to rejections by other jurisdictions as well as approvals. It has taken a long time for EU countries to accept European level decisions by EMA, and these are still not always accepted by all

more closely related to mutual coordination than to concatenate coordination, both because centralized activities may often exhibit greater mutual coordination than do decentralized activities and because praise is probably not properly read into most usages of *centralization*.

countries. As long as separate juri[s]dictions exist there is a danger that regulators will compete to attract applications and the resulting income. If procedures, timescales and fees are standardised the incentive to do this will be reduced, as will the need for separate agencies around the world.

Hutton's use of *harmonization* brings to mind his uses of *coordination* and *centralization* above. "Some" harmonization would be efficient, he says, but then seems to complain that separate "jurisdictions" continue to exist at all. As I wrote in response to the similar concern voiced by Randall Ellis, it is not obvious that "danger" lurks where permitters compete; indeed, inducing competition among the permitters is the very point of the reform. Hutton's concerns might be addressed by Kenneth Arrow's proposal that nations evaluate other nations' regulatory work.

At questionnaire's end, Hutton writes:

As a general comment, my own view is that decision-making on drugs and devices would be assisted by more and different information (e.g. on true effectiveness) and by more integration of licensing and reimbursement decisions. From a national health system perspective the problem may be seen as not enough cost-effective products rather than not enough products reaching the market. Changing the way FDA

makes decisions would be part of this process e.g. recognising that the trade-off between efficacy and adverse events is one which should be made transparently, and with input from patients. As the focus shifts towards a better-informed reimbursement decision, more FDA decisions would become conditional on further evidence, and its arbitrary ability to halt or delay approval would be reduced. The questionnaire did not allow discussion of these issues which underlay my answers.

By “more integration of licensing and reimbursement decisions,” it seems less that Hutton wants costs to be considered in approval decisions, but more that he is suggesting the (British) government could consider supporting relaxation of pre-market approval requirements given that it can use its reimbursement decisions to shape so much of the marketplace.

C. Daniel Mullins

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summoned as a member of the *Value in Health* and *PharmacoEconomics* editorial boards

Mullins strongly supports pre-market approval, and he emphasizes imperfect information as a rationale for the policy. He sees systematic erring both when consumers

cope with uncertainties and when doctors select therapies. When asked how consumer erring manifests itself, he writes: “Patients infrequently use evidence-based decision making strategies[.] Many patients are not able to comprehend and adhere to treatment recommendations (e.g. non-compliance, over/under dosing)[.] Most patients excessively discount future risks[.]”

Regarding “evidence-based decision making strategies,” most patients certainly don’t read scholarly journals or attempt to analyze clinical trial data; instead they base medical decisions on guidance from those they trust, e.g., doctors, pharmacists, drugmakers, retailers, non-scholarly publications, the FDA, and so on. Reliance on guidance in itself is no error; as I argued in response to Cornelis Boersma, division of knowledge is not a market failure. Patients who cannot “comprehend and adhere to treatment recommendations” are going to have as much trouble using approved drugs as they would using unapproved drugs, and so again (see my responses to Boersma and John Hutton) I fail to see a connection between persistence or adherence and pre-market approval policy. Accounting appropriately for future risk may be difficult, but (as I argued in response to Randall Ellis) it would seem to be even more difficult for a distant regulator bereft of situational knowledge.

To elaborate his claim of physician erring, Mullins writes: “Although many physicians practice evidence-based medicine, marketing by branded pharmaceutical manufacturers introduces a systematic bias towards prescribing of branded medicines,

even when the[re] is insufficient evidence of superiority to non-advertised therapeutic equivalents.” Such advertising may in fact be a good signal of quality (see my response to John Brazier), but if not, advertising could be regulated directly. And the pre-market approval apparatus itself may favor “branded medicines” by keeping off the market any ‘new drug’ that hasn’t been pushed through the expensive regulatory process by a (typically large) pharmaceutical manufacturer.⁵⁷ FDA’s recent granting to URL Pharma of marketing exclusivity for the widely used drug colchicine (Kesselheim and Solomon 2010) may illustrate the point well.

In addition to systematic error by doctors and patients, Mullins points to another instance of imperfect information that could justify pre-market approval: “The asym[m]etry of information between pharmaceutical manufacturers on the one hand and prescribers, patients, and other decision makers on the other hand reflects a market failure. This is counter-balanced in the current environment by FDA policy that requires manufacturers to promote their products according to the FDA-approved label.” Selective disclosure of research is a thorny matter, and the FDA’s gatekeeping power does enable the FDA to negotiate prespecified study methods with sponsors. But notice that the

⁵⁷ Large pharmaceutical firms experienced with the FDA approval process may have a sizable competitive advantage in terms of ability to gain approval for new drugs. “Firms covet the solid relationships of those few sponsors that continually win the FDA’s confidence. Smaller, newer companies seek out these firms for licensing agreements, hoping that a recognized firm with a predictable ‘machine’ for generating regulatory approvals will allow them to shepherd a new product to market” (Carpenter 2010, 663).

intervention suggested by Mullins to resolve the asymmetry is *not* pre-market approval (i.e., the banning of low-quality drugs) but is rather a restriction on manufacturer speech.

Question 11b reads, “*Say the policy that requires pre-market approval was eliminated and, in its place, a policy was implemented allowing new pharmaceuticals/devices and initially classifying them as requiring a doctor’s prescription (pending a review process to consider dropping the prescription requirement). Do you think such a liberalized system would be superior to the current system?*” Mullins chose No, because “Physicians do not have the time or resources to evaluate the enormity of evidence that allows a systematic review of the benefits and risks of drugs.” As in my responses to John Brazier and Anthony Culyer, I would argue that it is only necessary that physicians have a good sense of what expert analysts to trust, not that physicians do the analysis themselves.

Mullins does not support (in question 22b) the reform making approval automatic upon completion of FDA-specified testing, saying “There are many terminally ill patients who would be harmed by unsafe products that may be inaccurately viewed as pr[ov]iding sufficient potential value in terms of the possibility of cure.” I see Mullins making no claim for *systematic* error here, only one for error. He is thus trivially correct that such sad events will occur, as they do now. Are patients desperate to live more likely to be saved from lousy drugs by research and communication or by attempts to ban the drugs? Hopes can be pinned as easily to unsafe uses of approved products as to unsafe uses of

unapproved products, as the case of high-dose chemotherapy demonstrates (Brownlee 2008, 117-141). Furthermore, the effectiveness of law in constraining desperate patients is limited. As is openly acknowledged in the FDA's Regulatory Procedures Manual—an internal policy guide which “does not create or confer any rights for or on any person”—the agency under many circumstances will not enforce the ban on an unapproved drug against a patient with a “serious condition” who imports the drug for personal use.⁵⁸ Consider also that prominent (and sympathetic to pre-market approval) narratives on Laetrile, the purported cancer treatment that became a black-market phenomenon during the 1970s, peg their dénouement not to FDA's rejection of or enforcement actions against the drug—it was of course unapproved the whole time—but to the publicity given to results of a trial conducted by the National Cancer Institute (Young 1992; Carpenter 2010, 410-428).

Mullins also rejects the reform that would automatically approve for the United States market any drug approved in Europe, Japan, Canada or Australia. Asked “*Why*

⁵⁸ “In deciding whether to exercise discretion to allow personal shipments of drugs or devices, FDA personnel may consider a more permissive policy in the following situations: [...] 2. when a) the intended use is unapproved and for a serious condition for which effective treatment may not be available domestically either through commercial or clinical means; b) there is no known commercialization or promotion to persons residing in the U.S. by those involved in the distribution of the product at issue; c) the product is considered not to represent an unreasonable risk; and d) the individual seeking to import the product affirms in writing that it is for the patient's own use (generally not more than 3 month supply) and provides the name and address of the doctor licensed in the U.S. responsible for his or her treatment with the product, or provides evidence that the product is for the continuation of a treatment begun in a foreign country.” (FDA.gov 2010b).

not?” he replied, “First, the other regulators could make incorrect decisions. Second, there could actually be scientific reasons why the benefit/risk trade-off of a drug would differ across patient populations.” My critiques of Marc Berger and Anthony Culyer on this question apply here.

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Maniadakis, who strongly supports pre-market approval, says patients do not systematically err when coping with health uncertainties and that doctors do not systematically err in prescribing. He rejects the reform proposed in question 11b, “*allowing new pharmaceuticals/devices and initially classifying them as requiring a doctor’s prescription (pending a review process to consider dropping the prescription requirement).*” When asked “Why not?” he says:

It is very obvious. Perhaps we may lose some [of] the benefit with the delay but the safety benefit is significant. There are so many

[t]echnologies which are found to harm at[]the late stages of[]pre market ap[p]roval. What will happen if these enter the market and one or two years down th[e]line are proved to be harmfu[l]. There so many examples of technologies (COX 2 inhibitors) that are proven to have issues even with t[he] existing str[u]ctures in place. The risk would be high and the cost would be unacceptable.

Maniadakis's argument comprises nothing more than an observation that the current system catches some technologies that are "proved to be harmful." Instead of discussing "What will happen if these enter the market," Maniadakis is satisfied to pose the question rhetorically. He cites no evidence in support of his assertion that the benefits of pre-market approval outweigh its costs.

Maniadakis says uncertainty *per se* constitutes a market failure:

It is general[l]y a failure because consumers in this a[re]a are not like other consumers. I do admit though that nowadays, because of information, knowledge, institutions, providers and organisations in p[la]ce, is not so much an issue as it was in the past.

In addition to uncertainty, Maniadakis gives this additional sense in which imperfect information justifies pre-market approval:

Risk taking behaviours of some providers which are tryi[n]g to maximise financial and related objectives in t[he] short run.

How are consumers different with regard to health care? What are the providers' unfortunate risk-taking behaviours? My response to Cornelis Boersma on provider profit-seeking might be relevant to Maniadakis's concerns, but it's hard to know.

Maniadakis says public-goods aspects of knowledge are a source of market failure. In question 18b, he is asked "*Do you think that this source of market failure would be better addressed with a policy that subsidizes the generation of knowledge, e.g., via the National Institutes for Health?*" He says No:

It can be part of the p[ic]ture but can not be the solution. Who says that public institutions and their staff are doing the job better than the market?

The blackboard problem is simply that less of the public good is produced than is desirable. Appropriately, the solution proposed in the questionnaire—allocation of funding to the NIH—assumes that the NIH could help close the gap in quantity of knowledge (and therefore be "part of the picture" only), not necessarily that the NIH

could supplant inferior private research with superior public research. Maniadakis seems not to have understood the question in the manner intended.

In response to question 22b—*As compared to the current system, would you favor making approval of a new drug automatic upon completion of the safety and efficacy testing processes specified by the FDA, regardless of what those testing results turned out to be?*—Maniadakis says No:

Because [it] is not enough by any means. There [is] so little we know about their effects in that stage. It is so early in the process and the knowledge is limited, on average.

If the endpoint of the FDA testing process is still “so early in the process and the knowledge is limited,” then how does the FDA itself justify its selective bans?

Maniadakis’s answer is a crude form of Marc Berger’s notion that, because “evidence for benefits and harms is incomplete at the time of product launch,” an “advocate for the public” should at that time impose its “balanced interpretation of the available information.”

Question 24b reads: *“You indicated that a superior ability of government to assure the safety and efficacy of pharmaceuticals justifies the policy requiring pre-market approval. Does that superiority stem from the FDA having special expertise in evaluating*

safety and efficacy?” Maniadakis replied Yes. In response to the followup question, “*Why is it that doctors and consumers have inferior judgment in evaluating safety and efficacy?”*, he wrote:

Many reasons. Lack of data, expertise, time, sources, ability and many others. Can they replace an institutions such as FDA. Of course it needs to be pointed that their evaluations are important too, but later on on top of preceding assessments.

Yes, the FDA or a similar institution would be important in bringing resources and expertise to bear. But Maniadakis does not explain the distinctiveness of a government institution. Plus, the context of the question is pre-market approval, which is not merely the provision of “preceding assessments,” and in those cases where the FDA’s decision is to withhold permission for the product, doctors’ and patients’ judgment should not be said to enter in “later” and be “important.” See my criticism of Cornelis Boersma, who characterized the FDA as only delivering “[v]aluation of existing information/evidence.”

To a second probe, “*Would you say that impartiality or commitment to the public good are sources of the government’s superior ability to assure safety and efficacy?”*, Maniadakis also says Yes:

I am not arguing that this is always the case and that there are no exc[ep]tions to the impartiality and commitment. However, this is primarily the objective and in general is being achieved, not so m[uc]h because[] of the impartiality but because of the size and exp[ertis]e and resources.

Relative to consumers and most organizations, the FDA is large and well funded; it is also devoid of local knowledge and faces its own peculiar incentives, but Maniadakis doesn't consider that some advantages in decisionmaking may be held by doctors and patients.

Question 29b asks: *“As compared to the current system, would you favor a reform so that pharmaceuticals approved by the FDA counterparts in Europe, Japan, Canada, or Australia were automatically approved for the United States?”* Maniadakis says No:

Li[ke] so many things in life, medical science is not black or white and objective. It is down to the individual country and its experts, on the basis of many factors and considerations to judge whether a new technol[og]y is safe and ef[f]icacious for the specific population, relative to what is already available and known.

Here Maniadakis again puts forward a less nuanced version of an answer given by Marc Berger, seemingly stating a belief that the differences between the “specific population” of the United States and that of Canada, say, might make it sensible to permit a drug in one country but not the other. I wonder what an example of such a drug might be. Has anyone ever claimed that some particular drug is unsuitable for use in the United States and yet “safe and efficacious” for those Canadians who might elect to use it?

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Matuszewski strongly supports pre-market approval. In the closed-end question 5b, he selects all three suggested sources of market failure—“Imperfect information,” “Public-goods aspects of knowledge,” and “Government has superior ability to assure safety and efficacy”—and he also describes an “Other” source of failure:

US health care system subject to irrational decision-making due to conflicting forces dominated by income maximization

Matuszewski does not explain how “income maximization” leads to “irrational decision-making,” but perhaps he has in mind the sort of analysis given by Arrow (1963). Nor does he explain why the mechanisms identified by Arrow, e.g., physicians’ efforts to demonstrate trustworthiness, would be insufficient to remedy problems.

Matuszewski says Yes when asked in question 7b whether patients err systematically when coping with health uncertainties. When asked the followup question “*In what ways does consumer or patient erring manifest itself?*”, he writes: “Tend to self diagnosis, susceptible to marketing influences.”

Matuszewski does not provide evidence for the claim that the practice of self-diagnosis leads to systematic error, but if it does, it is hard to see a connection with pre-market approval. Perhaps there could be an indirect effect if pre-market approval increases confidence in medical science and its practitioners (see my response to Don Husereau). Prescription requirements, though, would be a more direct method of leading patients to the physician’s door. Other interventions that go more directly to the problem would be improving patient education and enhancing access to physician assistance.

“Susceptible to marketing influences” sounds similar to John Brazier’s concern about “well financed advertising campaigns.” While a manufacturer’s strategy of promoting substandard drugs could be expected to induce countervailing strategies by competitors, researchers, doctors, and patients, the notion of susceptibility suggests a

notion that consumers very often don't realize when they are being sold something. But common experience shows that consumers are more skeptical of advertisers than they are of news media and educators; why else would media and educators carefully guard their reputations and credentials? Media and educational messaging is not invulnerable to "marketing influences," but neither is government decisionmaking. As in my response to Pedro Pita Barros, I would ask why it is better to block voluntary transactions than to launch informational initiatives that attempt to counter bias directly.

Matuszewski also says doctors err systematically, saying those errors manifest themselves in doctors' "[g]eneral inability to keep current with medical literature and insidious effects of technology marketing and educational support." A doctor need not be current on the pharmacology literature to have a good sense of which expert advice should be trusted as input into his decisions, and a reformed FDA could provide a certification (as in Table 1's "Variant #1") in place of pre-market approval. Similarly, doctors could discount marketing to place an appropriate level of trust in the FDA certification, though the connotation of "insidious" (not unlike that of "susceptible") makes me think Matuszewski would argue that marketing often makes doctors misplace their trust. If so, though, a superior remedy might be to expose corrupt or feckless doctors, rather than to assume that the patients of such doctors are made significantly safer because a tiny slice of the vast set of situationally inappropriate treatments remain banned.

In addition to erring by doctors and patients, Matuszewski said there is another sense in which imperfect information may justify pre-market approval:

Health care in US [is] not universal, but rather subsidized in an [in(?)]efficient manner. Access and use of medical technologies varies widely across the country, along with expected outcomes. Cottage-industry structure of health care delivery and financing leads to market failures for large segments of the population[.]

Matuszewski here brings up the well documented geographic variations in medical practice and expenditures (see, e.g., Wennberg and Gittelsohn 1973; Finkelstein, Gentzkow, and Williams 2014). He does not, however, at all explain how these matters connect to pre-market approval policy.

In response to the first reform proposal in the questionnaire, “*Say the policy that requires pre-market approval was eliminated and, in its place, a policy was implemented allowing new pharmaceuticals/devices and initially classifying them as requiring a doctor’s prescription (pending a review process to consider dropping the prescription requirement). Do you think such a liberalized system would be superior to the current system?*” Matuszewski says No, because “Anecdotal evidence would replace scientific knowledge and such a system would be highly susceptible to industry inf[l]uences that might not be in the best interests of patient care.” Matuszewski seems here to assume

there would be no more publicly available information on clinical trials, but as I argued in response to Kenneth Arrow, some profit-oriented certification of safety and efficacy data should be expected. Furthermore, the question did at all specify that no government-led knowledge production could or would be carried out, only that new pharmaceuticals would be allowed.

When asked in question 18b whether a policy that subsidizes the generation of knowledge is better than pre-market approval as a solution to the problem of knowledge as a public good, Matuszewski said Yes. He did not, however, favor “*making approval of a new drug automatic upon completion of the safety and efficacy testing processes specified by the FDA, regardless of what those testing results turned out to be*” (question 22b), writing that “The safety of the general public requires the abil[i]ty to determine that certain risks are to[o] serious to allow.” This remark relates to Pedro Pita Barros’s assertion of the need for a “minimum quality standard,” and I refer the reader to my response there.

Matuszewski says that doctors and consumers have inferior judgment (relative to FDA) in evaluating safety and efficacy owing to a “[l]ack of focus on pure unbiased evaluation, general lack of time and expertise to conduct such e[va]luations, and large marketing pressure from technology industry, clinical peers, and patient advocacy groups.” Then, when asked if “*impartiality or commitment to the public good are sources of the government’s superior ability to assure safety and efficacy*” (question

26b), Matuszewski said Yes, adding that the FDA faces “[n]o conflicts economically and [is] able to consider societal perspective.” There are always some conflicts, and there is no “pure unbiased evaluation.” Even if Matuszewski were unaware of the Prescription Drug User Fee Act, he should understand generally that there is a relationship between FDA’s operating budget and its workload, which could make FDA more inclined to support whatever may serve to maintain or increase the flow of INDs and NDAs from industry.⁵⁹ Regarding the FDA’s ability to take on a “societal perspective,” Matuszewski must know that FDA often faces—and has arguably on occasion bowed to—intense pressure from the “patient advocacy groups” about whose influence on doctors and consumers he expressed concern. We should perhaps expect that a powerful, reputation-concerned agency will succeed in appearing to manage such pressures with equanimity, while doctors and consumers will appear buffeted and frazzled. However, as I wrote in response to Marc Berger, that a political process balances competing interests does not mean that its outcome is tantamount to wisdom. A “societal perspective” is worthy, but a perspective is more fully sensitive when it incorporates the myriad local features perceived only by local actors.

Matuszewski rejected automatic approval for drugs approved by foreign regulators. When asked “*Why not?*” he wrote: “US FDA process is still considered by most of the world as gold standard, which I believe it is.” The question is about the

⁵⁹ The Prescription Drug User Fee Act is often criticized for having increased the correspondence of the FDA’s economic interests and those of the pharmaceutical industry (see, for example, Angell 2004, 208-210; Hinchey 2005).

desirability of open competition in permitting drugs. To claim that the FDA is best of the existing permitters at this moment, in the absence of such competition, is to not engage that question.

G rard de Pouvourville

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Pouvourville strongly supports pre-market approval, finding a rationale for it in “[n]ot only imperfect information, but also complexity of information and need to protect the consumer.” He says neither consumers systematically err with regard to uncertainties, nor doctors when prescribing therapies, but uncertainty *per se* does constitute a market failure.

When asked “*How in your view does uncertainty per se constitute a market failure?*”, Pouvourville replies, “The question is ambiguous: most importantly it is not uncertainty *per se* alone but the asym[m]etric capacity of actors to deal with it, leading to opportunistic strategies which could kill people in the domain of medicines.”

Pouvourville is trivially correct that some actors are more sophisticated than others, but beyond that it is hard for me to see his point. Regarding the importance of medical

decisions and why that importance does not amount to a market-failure rationale, see my critique of John Brazier.

The questionnaire then probes for any other sense in which imperfect information is a source of market failure justifying pre-market approval. Pouvourville writes, “Again the question is as much imperfection as it is asym[m]etry of knowledge: even if Doctors are more and more educated they cannot cope with the growing complexity of knowledge required to develop a new drug.” Once again, the division of labor is not a market failure; to do well in choosing therapies, a doctor needs only develop a good sense of which pharmaceutical experts to trust and how to weigh their input. See my critique of Cornelis Boersma for a more thorough argument.

Question 22b asks, “*As compared to the current system, would you favor making approval of a new drug automatic upon completion of the safety and efficacy testing processes specified by the FDA, regardless of what those testing results turned out to be?*” Pouvourville chooses No, but when asked “*Why not?*” explains that he did not comprehend the question: “This question is again ambiguous, and does not allow for a yes or no answer. What does regardless of what those testing results turned out to be? mean? So I answer no because I do not under[s]tand either what an automatic approval would be unless it does not check for a correct balance of benefits and risks!”

Pouvoirville supports the reform automatically approving for the U.S. drugs that are approved by FDA counterparts.

At questionnaire's end, Pouvoirville offered this commentary: "FDA may be criticized and its processes may be too cumbersome, but there is no way one should go back to a situation when drug companies were marketing drugs the safety and efficacy of which [we]re not supported by goo[d] evidence. Perhaps there is a growing aversion to risk in our western societies which may impede the development of innovations, but this has to be carefully assessed." This seems to me like a more pointed expression of Karl Matuszewski's concern that liberalization is tantamount to a rejection of medical science. Even if "a growing aversion to risk" on the part of the public enabled the creation of the FDA, on what grounds should we grant that this was an appropriate political response, or even that the "risk" was properly perceived and addressed? Centralization of certification might itself be risky, an instance of putting too many eggs in a single basket; that it was not or is not popularly perceived to be such, is not much of an argument. Pouvoirville accords a large presumption to the status quo.

SYNTHESIS OF K&B SURVEY
RESPONSES SUPPORTING PRE-MARKET APPROVAL

Do leading health economists who support pre-market approval have a handle on the basic truths surrounding the issue? How intelligent are their formulations? Are they persuasive when identifying central tradeoffs?

Below I attempt to summarize the economists' responses into what I see as the most common or pivotal arguments for pre-market approval, loosely ordered from strongest to weakest. I explain why I find even the stronger arguments to be incomplete at best. I show that, even though the economists were prompted to mention scholarly evidence in support of their claims that patients or doctors err systematically with regard to selection of treatments, hardly any such evidence was introduced—and I cite some evidence suggesting that, with regard to other prominent government interventions, a sizable share of professional economists tend to know offhand what literature supports the intervention. And I claim that the economists surveyed do in fact have reasonable prominence in the field of health economics.

Key formulations or arguments for pre-market approval

Doctors misplace their trust

Several economists (Berger, Boersma, Brazier, Culyer, Ellis, Husereau, Hutton, Maniadakis, Matuszewski, Mullins, Pouvourville, Scherer) said that patients or doctors lack the resources, such as time and intelligence or wisdom, to analyze drug information. There is of course a division of labor, so we are not disturbed when a doctor does not himself conduct every aspect of every study on every drug he prescribes. What would be worrisome is to find that patients and doctors, when seeking guidance, *misplace their trust*. And some of the economists are worried, saying doctors are susceptible to unfortunate influences such as psychological biases (Husereau), reluctance to follow evidence or guidelines (Boersma, Culyer, Hutton), marketing (Matuszewski, Mullins), or desire for profit (Maniadakis). But still there is a missing piece, a piece that none of these economists supplied: Why are we to believe that these tendencies to err are well, to say nothing of best, remedied by the particular policy of pre-market approval?

With regard to patients, it is unclear why worries about patient error are not resolved through prescription requirements. It would seem hard to justify pre-market approval on the basis of patient error if physicians were believed capable of making appropriate prescriptions—and indeed, all 14 economists discussed in this paper rejected the reform, proposed in question 11b, that would replace pre-market approval with

prescription requirements on all new drugs. However, six economists (Arrow, Berger, Culyer, Scherer, Maniadakis, Pouvourville) said in response to question 9b that doctors do *not* systematically err when selecting and prescribing therapies. It is worth reproducing here the four strongest of the answers produced by those six economists to question 12b, which asks them why they rejected the question 11b reform that would replace pre-market approval with prescription requirements on all new drugs:

Table 4. The strongest answers in response to question 12b from those economists who in question 9b say that doctors do not systematically err

<p><i>“Why [do you] not [think a liberalized system allowing new pharmaceuticals/devices and initially classifying them as requiring a doctor’s prescription would be superior to the current system]?”</i></p>
<p>Kenneth Arrow: “There would be no publicly available evidence on the efficacy and safety of the drugs, except what is supplied by interested parties.”</p>
<p>Marc Berger: “The government has a legitimate role in ensuring that the information disseminated to physicians and patients is accurate and fair. The evidence for benefits and harms is incomplete at the time of product launch and is therefore open to interpretation. The FDA acts as the advocate for the public to ensure a balanced interpretation of the available information.”</p>
<p>Anthony Culyer: “Most doctors not qualified to evaluate evidence of efficacy or risk of harm. Most doctors have irrational attitudes to risk. I prefer evidence-informed prescribing.”</p>
<p>F. M. Scherer: “Your earlier question asked whether physicians systematically err; I replied no. But they do err randomly, and frequently, in large measure because they are simply so busy that they don’t have time to consider indications and contra-indications. Also, there are informational economies of scale in having an agency like the FDA consider in detail, however imperfectly, all the evidence available on indications and contra-indications. Most physicians simply don’t have time to do this.”</p>

I believe that Culyer, contrary to his answer to question 9b, suggests here that doctors do in fact err systematically. And so I think it is fair to say we have a majority of the 14 economists (the eight who said yes to question 9b, plus Culyer) holding that doctors are erring systematically when they make prescriptions. I think this claim raises a vital question: What exactly is it that we need doctors to do?

In addition to prescribing drugs, doctors also perform procedures and tests, and make diagnoses. The choice to perform a procedure or order a test is a decision very similar to a drug recommendation or prescription, yet medical tests and procedures are not subject to comparably intense regulations—and none of the surveyed economists suggested that they should be. And doctors need a great deal of intelligence or wisdom, coupled with time to learn and stay up with medical science, in order to make diagnoses (Phelps 2000, 237-248); furthermore, pharmaceutical companies have been known to promote the diseases that their drugs purport to treat (Moynihan, Heath, and Henry 2002). So do our economists believe that the government should mandate the use of a particular diagnostic manual and place a ban on unlisted diagnoses? These ideas for the extension of pre-market approval concepts to procedures, tests, and diagnoses are not, to my knowledge, discussed by mainstream American politicians, and, perhaps accordingly, they have hardly been raised in scholarly literature.⁶⁰ However, these ideas should be

⁶⁰ Fuchs (1974, 118), in a passage critical of pre-market approval, speculated on “what would happen if the regulatory standards that are applied to drugs in the United

obvious ideas to any analyst *who takes the notion of physician incompetence seriously enough to believe it justifies the entire FDA pre-market approval apparatus*. Such an analyst should have thoughts to offer about our reliance on physicians to make diagnoses, order tests, and carry out procedures: ‘Of course, we do rely on doctors to do X, Y, and Z even in the absence of federal rules governing X, Y, and Z, but that works because...’ Or, perhaps, radically: ‘We need the federal government to do much more towards the regimentation of health care practices.’ None of the surveyed economists offered any such thoughts, but, neither did the K&B questionnaire press them on the point.⁶¹

Maybe physician incompetence justifies pre-market approval. But if it does, then I would think it could justify other interventions that do not exist under the status quo. In that event, to mount a defense of pre-market approval on the grounds of physicians’ general incompetence is an act with radical implications for policy. Victor Fuchs, in a book still assigned in health economics courses at top universities today, made this point forty years ago:

States were also applied to surgical procedures.” Phelps (2000, 258) merely noted that “Inventors of new [treatment] strategies...face no liability for creating a bad strategy. Only the doctor who uses the strategy (on a case by case basis) has any potential liability for harm that comes from using a bad strategy.” Phelps (2012, 465-466) added that “the considerably different treatment of drugs specifically (under the FDA law) and ‘medical interventions’ in general...creates an odd schizophrenia in the production of knowledge and in the likelihood that a new treatment innovation will reach the market.” *Cf.* Lindstrom (2002), who argued that “the policy reasons for regulating to ensure the safety and efficacy of drugs and devices apply with equal force to the argument that the FDA should also regulate medical procedures in the same manner.”

⁶¹ Klein and Tabarrok (2008) press physicians on a similar matter, asking those who support both the pre-market approval of new drugs and the liberal rules governing off-label usage of approved drugs to justify the seeming inconsistency.

Under law a patient cannot obtain [prescription] drugs without a physician's prescription. No physician is under any compulsion to prescribe a drug unless he believes that its possible therapeutic benefits outweigh possible harm. Moreover, patients still have recourse to malpractice suits in cases of the physician's gross negligence.

The present approach of strict market controls on drugs really amounts to a vote of "no confidence" in physicians' ability to prescribe with judgment and care. If such a vote is warranted, it raises serious questions about the state of medical education, the organization of medical practice, and the usefulness of medical licensure.

A critical question for social choice in the drug field at this time is whether the United States should continue to place heavy emphasis on barring potentially unsafe drugs from the market at the cost of possibly delaying the introduction of helpful new drugs. A policy of extreme caution hardly seems warranted a priori since human lives are at stake either way the choice is made. If physicians are in fact ill equipped to function within a more permissive regulatory framework, perhaps the solution lies in the reform of medicine rather than in regulation of drugs.

(Fuchs 1974, 118-119)

But there is no overt radicalism in the survey responses from the economists above. Perhaps the economists would have, if pressed, explained how the domain of physician incompetence is in fact limited, and that while its logic applies to prescribing it does not carry much further.

What could account for systematic error by physicians in the realm of pharmaceuticals, but not beyond? One plausible candidate is marketing of drugs by pharmaceutical firms, as there may be less or no marketing of tests or procedures. But the effect of marketing relates to the entire universe of drugs, both new and old. Marketing is certainly often intense with regard to new drugs. Perhaps physicians are more susceptible to marketing of *new* drugs, about which less is known and around which there might also be hope and excitement. But it seems implausible that physicians would be particularly susceptible to the marketing of low-quality drugs. As I wrote above in response to Brazier: “This might justify an intervention that improves knowledge about or restricts those drugs that are *newer*, but pre-market approval bans drugs that the regulator has not rated highly in an assessment of *quality*.” Drugs that the FDA deems ‘safe and effective’ are still dangerous when prescribed too often or otherwise incorrectly, and we rely on doctors to avoid those errors not only in the midst of a ballyhooed ‘product launch’ but also thereafter.

Knowledge is too expensive to communicate to doctors

Culyer aside, the other three economists quoted in Table 4 clearly claim that pre-market approval has a positive *knowledge* effect—the FDA supplies “publicly available evidence” (Arrow), it ensures “a balanced interpretation of the available information” (Berger), and it considers “all the evidence available on indications and contra-indications” (Scherer). This raises a very different question: Why is the banning of some products on quality grounds necessary to get these positive knowledge effects? And here, fortunately, the K&B questionnaire asks appropriate followup questions: question 22b proposes that new drugs be tested by the FDA but approved regardless of the test results. Arrow, Berger, and Scherer all reject this reform, and here’s why:

Table 5. Responses from three of the economists listed in Table 4 to question 23b

<p><i>“Why [as compared to the current system, would you] not [favor making approval of a new drug automatic upon completion of the safety and efficacy testing processes specified by the FDA, regardless of what those testing results turned out to be]?”</i></p>
<p>Kenneth Arrow: “This is a closer call than the abolition of the approval process. Nevertheless, the dissemination of the relevant information is too costly for the patients (and the doctors) to permit the sale of drugs that have not met the appropriate standards. (There are many parallels in other fields.)”</p>
<p>Marc Berger: “The government has a legitimate interest in the public health and safety. If a new product is less effective and is associated with more harms than available treatments, the government appropriately should not allow it to be marketed.”</p>
<p>F. M. Scherer: “The historical record is clear: FDA has made serious errors, and physicians have in large numbers prescribed</p>

the approved drugs. So the system is imperfect. But without the informational function the FDA performs, there would be even more prescribing errors.”

Scherer seems to dodge the question outright, while Berger merely asserts that the status quo is appropriate. Arrow makes an argument—that dissemination of the information is too costly. But doctors are provided with all manner of information about the universe of approved drugs, and we rely on them to process that information sufficiently to select drugs from that universe. What is the supposed difficulty that would be encountered in offering to doctors information about a larger universe of drugs?

Prohibition is benign

A few economists (Boersma, Brazier, Scherer) were evasive in responding to the questions that most pointedly isolated, and proposed to relax, the prohibition on unapproved drugs that lies at the heart of pre-market approval policy. I have interpreted this evasiveness as a form of denial that pre-market approval is coercive, in the sense that it forbids certain voluntary exchanges. Daniel Klein and Stewart Dompe (2007, 151-158) show that most economists who support minimum-wage laws hold that those laws are not significantly coercive, and I conjecture that most economists who support pre-market approval view it similarly. With regard to pre-market approval, however, such denial is much harder to understand given that many persons have been subjected to harsh criminal penalties for the sale or possession of illegal drugs, a circumstance with direct

connections to the policy of pre-market approval.⁶² Given that pharmaceutical policy carries such serious consequences for so many, analysts should take care to distinguish policies that are informational or educational from those that are restrictive or prohibitionist.

Those economists who did acknowledge the coercive aspects of pre-market approval generally seemed to view those aspects as representing something of a free good, i.e., they seemed not to place any value on the reduction of coercion that would be achieved through liberalization. The attitude seems to be: After all the work is done to identify low-value products, failing to ban them would be tantamount to leaving a twenty-dollar bill on the table. It is as if these economists believe the only effect of such a ban is to prevent certain poor choices by consumers. But a myriad of other effects must exist. For example, the paths down which scientific research proceeds are different under pre-market approval, e.g., as when further study is discontinued on a drug that for whatever reason is not expected to garner approval, or when researchers mold their thinking in such a way as to mesh with regulator expectations. For another example, pre-market approval surely has some general effects on consumer confidence, probably

⁶² “FDA has not approved marijuana for medical use in the United States. [...] Under the Controlled Substances Act (CSA) Congress listed marijuana in Schedule I. Schedule I substances have a very high potential for abuse, *no accepted medical use in the United States*, and lack accepted safety data for use under medical supervision. [...] Pursuant to the FD&C Act, FDA is responsible for the approval and marketing of drugs for medical use, *including controlled substances*. [...] The criminal penalties related to Schedule I controlled substances are far greater under the CSA than those available under the FD&C Act for the distribution of an unapproved new drug.” (Meyer 2004, my emphases)

serving to increase confidence for many, possibly to a point beyond or even well beyond what may be justified. So product suppression, epistemic monopoly (Koppl 2010), and overconsumption are possible negative consequences of a product-banning regime such as pre-market approval. A convincing advocate for pre-market approval would acknowledge these possible consequences, even if ultimately to conclude that they do not outweigh the benefits of the policy.

Phantom validation

An alternate explanation for the failure to consider alternatives to product bans is that our economists are surreptitiously placing high value on what Klein (2008, 333) calls “phantom validation.” The economists may believe that an admission that government’s knowledge is insufficient to justify a ban is tantamount to an admission that there can be no ultimate validation of our choices, that no parent figure is there to take final and true responsibility for unfortunate events. This latter admission may be politically unacceptable or taboo, given contemporary democratic pressures (Buchanan 2005). What proceeds is the ensconcement and lifting up of a coterie of ‘experts’ who are tasked by the general public with the making of difficult decisions and the bearing of symbolic responsibility.⁶³ The tradeoff for the public may be poorer health outcomes in return for

⁶³ I am somewhat uncomfortable with my use of *responsibility* here. It might be more accurate to say that the experts are tasked with accepting *blame*, should things go wrong. Klein (1998b, 25-26) distinguishes two senses of responsibility: “the personal trait of being admirably responsive” and “the social-relations trait of holding the

reduced feelings of uncertainty and guilt. Needless to say, the possibility of such a tradeoff is rarely if ever acknowledged.

The regulator is evidently excellent

A few economists asserted or implied that the regulator is simply “independent” (Boersma and Brazier; Hutton also spoke of “independence”), “transparent” (Boersma), or not “interested” (Arrow), facing no economic “conflicts” (Matuszewski). Lacking elaboration, it is hard to see such assertions as meaning anything more than that the regulator is *governmental*. And yet: *independence, transparency, and uninterestedness* are hardly qualities that one could associate universally or uncontroversially with government agencies. The FDA has been criticized over and over regarding its levels of political independence, transparency, and entanglement with interested parties (see, e.g., Flanigan 2012, ch. 9). I judge these criticisms to be substantive and worthy of discussion. In his published work on the FDA, Daniel Carpenter (2010) takes the criticisms seriously, but still he supports pre-market approval (see Carpenter 2009c). Those among the

individual to account.” To have *responsibility* implies that one will be *held responsible* for poor outcomes, and being held responsible suggests that the person will face definite consequences for his action or inaction; as Klein elaborates, his “individual responsibility” means “government-administered systems of accountability for citizens” (ibid., 27). By contrast, we do not necessarily expect, upon hearing that someone is *to blame* for poor outcomes, that consequences must be forthcoming. Klein (ibid., 25-26) labeled his two senses of *responsibility* as “personal responsibility” (responsiveness) and “individual responsibility” (facing consequences). To these I might propose adding “symbolic responsibility,” meaning: the one who bears symbolic responsibility is the one who takes the blame from others.

surveyed economists who simply declare the FDA “independent,” etc., offer nothing resembling Carpenter’s more advanced formulations regarding conflict of interest.

At least one economist (Culyer) failed to mount even a minimally comparative analysis; he pointed to ways in which the market fails to deliver absolutely good results, but he said nothing even about how pre-market approval is supposed to improve results, let alone about how other possible interventions might work. The underlying attitude may be that we are to rely on the regulators’ judgment—that an economist’s job is only to identify or affirm problems, and it is the regulator’s job to consider and implement responses. I would say instead that economists and regulators should try to get on the same page with regard to both failures and remedies.

The individual and the nation are the only meaningful units of analysis

Several economists (Berger, Maniadakis, Culyer, Mullins) evinced a crude nationalism when reacting to question 29b, which proposed a denationalization of drug approval policy. Each of these economists put forth the belief that, *because* populations or cultures differ, denationalization of drug approval is inappropriate; none of these explained why it is that only cross-*national* differences in population or culture can justify differing approaches to pharmaceutical availability. By contrast, two others (Arrow, Scherer) who opposed denationalization made plausible arguments against it,

one preferring a global regulator to the scheme proposed in question 29b and the second claiming that economies of scale favor regulation at the national level.

The choice is not between unaided and hapless “individuals” and a national regulator who brings to bear a “variety of expertise” (Boersma) in deploying a “more thoughtful approach” (Husereau). If these are the stipulated facts, then in a two-choice world we surely should opt for nationalized decisionmaking! But “individuals” who need to make decisions can rely on others’ knowledge, including knowledge produced by groups, organizations, or government agencies. And government panels can make unwise or politicized decisions.

Few appeals to authority

When economists support an intervention, very often there is specific literature to which they will appeal as evidence for their position. For example, Klein and Dompe (2007) surveyed economists who had signed a petition to raise the minimum wage. Of 95 respondents to the Klein and Dompe survey, 90 agreed with a statement that such an intervention “would generate net benefits for workers and the overall economy through its effects on labor market mechanisms”—and, of those 90, over half were, when asked to do so, able to provide “one or two sources of information” in support of that belief,

including 29 respondents who cited specifically the work of economists David Card and Alan Krueger (Klein and Dompe 2007, 140, 143-144). If one were to take the Klein and Dompe study as representative, the takeaway is that one-third of economists who favor increasing the minimum wage, when prompted for evidence in support of their position, would supply *the same scholarly evidence*.

In questions 8b and 10b of the K&B questionnaire, economists who said either that patients or doctors systematically err in selecting treatments were asked: “*In what ways does [consumer or patient (8b), or, doctor (10b)] erring manifest itself? (If possible, please cite relevant evidence.)*” Of the 14 economists examined here (again, these 14 being all of those who support pre-market approval, believe there is a market-failure rationale for it, and were responsive to K&B’s open-ended questions), 11 encountered either question 8b or 10b, all 11 of whom encountered question 8b and eight of whom encountered both. Of these 11 respondents, only two (Husereau and Ellis) cited any evidence; one of these two respondents provided a single citation, and that citation was not among the multiple citations provided by the other respondent. Further, all of the citations were to studies in behavioral economics—*none were to research on pre-market approval of pharmaceuticals*. And, those two respondents aside, only one other respondent invoked any external authority in response to any other question (Scherer, who mentioned Marcia Angell in his response to question 19b).

This result tends to affirm the claim by Klein (2008) that there is nothing like a rigorous, well understood body of work that defends pre-market approval and that has withstood scrutiny by health economists over a number of years. More pointedly, there is little here running counter to the following proposition: Published scholarship on pre-market approval is not the basis for economists' support of pre-market approval.

A reasonably distinguished group

Perhaps the K&B sample is just very unrepresentative, or there was a response bias, with the result that respondents to the questionnaire are neither knowledgeable nor prominent in the field of health economics. Were it true, that would surely explain why many arguments put forward by the K&B respondents who support pre-market approval may be weak or not buttressed by scholarly evidence. However, it seems to me that the 14 economists discussed above are in fact a reasonably distinguished group, even leaving Kenneth Arrow's pre-eminence and Nobel Prize out of it:

- By country: USA (6), UK or Canada (4), other Europe (4)
- U.S. university affiliations (4): Stanford, Harvard, Maryland, Boston U.
- UK university affiliations (3): York (2), Sheffield

- Editorial board memberships: *Value in Health* (4), *Journal of Health Economics* (3), *Applied Health Economics and Health Policy* (3), *Health Economics* (2), *PharmacoEconomics*, *European Journal of Health Economics*
- Two editors of Elsevier's *Handbook of Health Economics* (Culyer and Newhouse 2000; Pauly, McGuire, and Barros 2012)

ENGAGEMENT WITH LITERATURE ON
MARKET FAILURES RELATED TO PRE-MARKET APPROVAL

My aim is to identify the common understandings among health economists as to what it is that justifies pre-market approval. To see if any market-failure arguments for pre-market approval are missing from the synthesis of K&B survey responses above, I have systematically reviewed relevant reading materials assigned in health economics courses at top universities. My method is documented in Appendix B. Below I discuss the justifications of pre-market approval found during that systematic review. I also discuss those other prominent relevant publications of which I am aware, such as those gathered in Klein (2008).

Unlike the justifications given by the respondents to the K&B survey responses above, the discussions of pre-market approval found in the literature and considered below are often provided by authors who oppose pre-market approval or whose stance on pre-market approval is unknown. In what follows I write as if the author is putting forward the justification, but often they may merely be reporting on a justification offered by others.

Sam Peltzman (1974)

In his 1974 monograph, Peltzman offered a rationale for pre-market approval that an observer of the events leading to its adoption by Congress might ascribe to its supporters. He saw two main events as having spurred the intervention: “The 1962 amendments to the 1938 Food, Drug and Cosmetic Act and the subsequent implementing regulations reflected both the concerns raised in the Kefauver hearings and those arising from the thalidomide episode” (Peltzman 1974, 8).

Drawing primarily on a report by the U.S. Senate Subcommittee on Antitrust and Monopoly (1961), Peltzman attempted to summarize the concerns raised there:

The initial impetus for changing the 1938 law came from hearings begun in 1959 by Senator Estes Kefauver’s Antitrust and Monopoly Subcommittee. Underlying these hearings was a belief that prevailing regulation permitted the introduction of new drugs of dubious efficacy that were sold at unusually high prices. This was said to result from a combination of patent protection for new chemical formulas, consumer and physician ignorance, and weak incentives for physicians to minimize patient drug costs. It was argued that drug companies devoted inordinate amounts of research to the development of patented new

drugs which represented only a minor modification of existing formulas. The companies would then, it was said, exploit the patent protection by expensive promotion campaigns in which extravagant claims for the effectiveness of the new drug were impressed upon doctors and (sometimes) patients. Since most doctors were thought to lack the pharmacological expertise necessary to evaluate new drugs, it was believed that they relied heavily on information supplied by the drug companies. It was argued that they frequently treated this information with insufficient initial skepticism. Moreover, they seemingly would have little incentive for a careful evaluation of drug company claims since prescription costs were borne by their patients. It was said that some patients who might otherwise question the cost-effectiveness of drugs prescribed for them appeared to be entranced by accounts of the curative powers of new drugs, so that they frequently pressured the more skeptical doctors to prescribe these new drugs.

Even where patent protection was weak, as for new products that were combinations or duplicates of existing chemical formulas, it was argued that consumer ignorance and weak cost-minimization incentives made artificial product differentiation an attractive strategy. Since the patent laws provided some incentive to differentiation by chemical formula, physicians were faced with a mentally taxing array of complex chemical names from which to choose. It was said that this produced a

reliance on easily remembered brand names, and that this, in turn, stimulated drug companies to concentrate on the promotion of easily remembered (and expensively promoted) brand names for old as well as new chemical formulas.

The Kefauver hearings characterized much drug innovation as socially wasteful. The waste was said to arise from product differentiation expenditures in an imperfectly competitive market permeated by physician ignorance: product differentiation expenditures were incorporated in prices which therefore did not reflect the “true value” of the drug to the consumer. It was argued that only in hindsight would doctors or patients discover that claims for new drugs were exaggerated: consumers would have been better off if they had used lower-priced old drugs (especially unpatented old drugs and most especially non-branded unpatented old drugs) instead of the new drugs. They would have paid less for treatment at least as effective as what they received. This view of the drug market was summarized at the Kefauver hearings by a former drug company medical director:

industry spokesmen would have us believe that all research is on wonder drugs or better medicinal products. They stress that there are many failures for each successful drug. This is true. ... The problem arises out of the fact that they market so many of their

failures. ... Most [industries] must depend on selling only their successes. ... [But] with a little luck, proper timing, and a good promotion program a bag of asafetida with a unique chemical side chain can be made to look like a wonder drug. The illusion may not last, but it frequently lasts long enough. By the time the doctor learns what the company knew at the beginning it has two new products to take the place of the old one.⁶⁴

Senator Kefauver concluded that accurate information about new drugs would be provided only if the government regulated manufacturer claims of effectiveness. A proposal to institute such regulation was included in a bill he sponsored in 1961, and a modification of the proposal was incorporated in the 1962 amendments. (Peltzman 1974, 6-8)

Peltzman's account offers a complicating variation on the *doctors misplace their trust* formulation, which is that pressure by patients, who can "be entranced" by "accounts of the curative powers of new drugs," can lead skeptical physicians to prescribe such drugs inappropriately. I interpret this as equivalent to John Brazier's speculation about "a tendency for consumers to believe a new treatment is better," but

⁶⁴ The quotation is attributed in the Subcommittee report to Dr. A. Dale Console, "formerly medical director of Squibb" (U.S. Senate 1961, 127).

now with the reason for such tendency specified as ‘entrancement’ that is unrelated to a lack of information or to a defensible interpretation of information. If excitement around a new product has such an effect, how can it be countered? This is, still, a problem that would apply to all new products (or at least the entrancing ones), and not specifically those that would pass a quality evaluation. Aggressive dissemination of knowledge by the regulator may not work, at least not while the product remains ‘new’. Could the regulator restrict new products in such a way that improves the situation? A blanket delay on all product introductions on these grounds may be pointless, because such might simply put off the day on which a product would be ‘new’ and entrancing. A possible intervention that comes to mind is to have new products for a period have their prescriptions be subject to an extra level of scrutiny, such as approval from a special board. That could mitigate the effects of ‘entranced’ patients on the process while allowing the clock to start ticking on the product’s perceived novelty, and buying more time to spread knowledge of the drug. But surely, the contemplation of such a policy would benefit greatly from a gathering of evidence about the supposed patient ‘entrancement’ by new drugs.

Peltzman then, drawing on the account by Richard Harris (1964), added a summary of additional concerns prompted by the thalidomide tragedy:

It is doubtful that the 1962 amendments would have been enacted without the thalidomide episode of 1961–62. Thalidomide was, in fact, kept from the U.S. market by the FDA under provisions of the 1938 law.

However, the manufacturer had distributed the drug to some physicians for experimental purposes. The 1938 law permitted distribution of this sort to those deemed by the manufacturer to be “qualified experts” as long as the drug bore a label warning the expert that it was still under investigation. The American manufacturer of thalidomide ended investigational distribution of the drug and withdrew its NDA after reports that deformed babies had been born to European mothers who had used the drug during pregnancy. These reports aroused concern that clinical testing of new drugs was insufficiently regulated. The lesson of the thalidomide episode appeared to be that, in the rush to market new drugs, producers were exposing humans to potential harm before that potential harm could be adequately evaluated. (Peltzman 1974, 8)

The thalidomide “episode” was an overt disaster. Can the potential for such a disaster be a form of market failure? The examples of Elixir Sulfanilamide and thalidomide are instances of many patients consuming drugs that were thought safe and effective, but proved unsafe. While neither drug seemed to promise particularly large benefits—Elixir Sulfanilamide was merely more pleasant to consume than alternative formulations, and it is hard to say that thalidomide, a sedative, was prescribed for critical indications—the active ingredients were considered effective for their indications. Possible remedies that readily come to mind include: basic testing of new products for safety (and testing of batches of ‘old’ products as they are manufactured), banning of

those that are clearly unsafe, requiring extra testing and giving strong voice to doubts about safety when such exist, and studies of widely used products to check their safety with regard to problems that clinical testing is not capable of detecting.

Sadly, we cannot conclude that these remedies will work simply because they come readily to mind; worse, there is a potential for such interventions to contribute to disasters rather than prevent them. Assume for the moment that, in the absence of the intervention banning unsafe products, consumers would be able to access, and would use appropriately, accurate assessments of the risk of new products—and also assume that the imposition of such intervention would create a widespread belief that all available drugs are “safe and effective.” Under such assumptions, a bad drug goes unconsumed in the world without the intervention—but in the world with the intervention, an error by the regulator with regard to a bad drug leads to an overt disaster. Under the same assumptions, regulator error with regard to a good drug creates the ‘statistical’ disaster of benefits foregone. These assumptions are of an extreme, arguably implausible form—accurate assessments under ‘the market’ system, yet the possibility that the regulator will err—but one could obtain similar results by relaxing the assumptions greatly. There is plainly a large range of assumptions about consumer assessments, research paths, confidence effects, patient heterogeneity, likelihood of regulator error, etc., such that when certain interventions are in place, drugs are unfortunately misused, overconsumed, or underprovided relative to what would happen in the absence of the interventions.

Fiona Scott Morton and Margaret Kyle (2011)

Morton and Kyle (2011) offer this market-failure rationale for pre-market approval in a handbook chapter on “Markets for Pharmaceutical Products”:

Pharmaceuticals may be considered “experience” or “credence” goods, for which the consumer has less information about quality than the producer. A patient is usually unable to determine whether a pill is safe and effective just from examining it, and sometimes even after consuming it. As is well known in economics, this information asymmetry can lead to the “lemons problem” described by Akerlof (1970), wherein the quality of the product falls to inefficiently low levels. One solution to this market failure is the provision of information about a product’s quality from a trusted third party, or, in the case of pharmaceuticals, a government agency’s regulatory approval process. (Morton and Kyle 2011, 765)

Post-market surveillance of safety in both the United States and Europe is a key component of drug regulation. Given that clinical trials are only able to assess a drug’s impact on a small subset of the population at

large, many of a drug's side effects are not known until it is released into the market. ...

Post-market surveillance is arguably most concerned with the safety of the approved drug, given that it is being used by a population much larger than that used in pre-approval clinical trials. The FDA requires all drug sponsors to support reporting systems where physicians or other providers can report adverse drug reactions and other reportable events. A survey of drug manufacturers found that mean spending on post-marketing safety per company was \$56 million (0.3% of sales) in 2003. The innovator must submit a report to the FDA within 15 days of a report of an adverse reaction to a drug. The FDA also maintains Medwatch, a website that allows consumers to submit complaints about the safety of drugs currently on the market. FDA officials investigate the claims and take action against drug sponsors accordingly. Criticism of post-marketing surveillance in the US has focused on the FDA's lack of sufficient authority to ensure compliance with post-marketing requirements as well as the general underreporting of adverse effects. There are few economic studies in this interesting area. (Morton and Kyle 2011, 767)

Its cost structure—large fixed and sunk costs of drug discovery and development and relatively low marginal costs of production...—is

another important feature of the pharmaceutical industry. Imitation costs are also quite low: once a product is known to be safe and effective, it can be backward-engineered with little difficulty. If competition from imitators drives price down to marginal cost, as standard industrial organization models would predict, then firms would be unable to recoup the fixed and sunk costs of development and thus would not engage in risky innovative activities. Of course, many other industries share these features, such as movie production, book publishing, and software. A key difference between the pharmaceutical industry and these others is that the social cost of a bad drug brought to market is considerably higher than the cost of a bad movie, which is a justification for its extensive regulation. (Morton and Kyle 2011, 772)

Analysis of alternative market designs to spur particular kinds of innovation is a promising area of research. Another area of research interest is the problem of eliciting information from private parties on the performance of drugs. For example, many drugs are used “off-label.” A physician may prescribe a drug for a use unapproved by the FDA (assuming the drug has been approved for a different use), which happens when the physician has a reason to think that the drug may be efficacious despite the lack of FDA approval. For example, relatively few drugs have been tested in children, so a great many pediatric

prescriptions are off-label; obstetrics is also a specialty with a lot of off-label prescribing. Without a financial incentive, the innovator will not bear the expense of an additional clinical trial in order to prove the new indication is valid. This may occur if the new use is discovered when the patent has too few years remaining on it to allow for significant sales after time is allocated for trials and FDA approval. However, if the innovator lacks FDA approval for its new indication, it may not legally market the drug for that use. So the innovator faces a trade-off between the cost of the trial and the incremental gain from marketing the new use to physicians. The nature and amount of existing research evidence for the new use may also affect the trade-off.

When the innovator chooses not to carry out the trial, social welfare can be harmed because physicians either may not want to prescribe the drug absent guidance, or do prescribe the drug, but without the knowledge of efficacy, dosing, and side effects that would be gained from a large randomized clinical trial. In the US there are currently limited regulatory mechanisms to get around this problem. A new indication can be patented—and the indication can even have orphan drug designation—so that other versions of the molecule may not list that indication on their labels. However, that does not stop physicians from prescribing a generic for the patented indication and depriving the innovator of rents, because off-label prescribing is legal. In addition, an

additional 20 years of patent protection for a new indication may be inappropriate, since the original product represents a more significant inventive step.

Subgroups of the population may benefit more or less from an approved drug. As with off-label use, there is no incentive for the innovator to conduct a trial to find those subgroups. This is because the firm is likely to lose sales from other subgroups when it determines which group of patients gains most from the drug. This is also an issue in the development of diagnostic tests to identify subpopulations. There is little academic work on the incentives in this system, and little on the design of regulatory mechanisms that might raise social welfare, either in a single-payer system or a market-based system like the US. Yet these are important topics. (Morton and Kyle 2011, 785)

I see Morton and Kyle as providing essentially two justifications, which they may or may not have intended to be connected: that pharmaceuticals are “credence goods” which are subject to the “lemons problem,” and that “the social cost of a bad drug brought to market is considerably higher than the cost of a bad movie.” With regard to the matter of pharmaceuticals being “credence goods” they immediately note that the remedial intervention in the industry is an unusual “regulatory approval process” and not merely provision of information about a product’s quality from a trusted third party.” Only seven pages later do they mention a distinctiveness in pharmaceuticals that could,

perhaps, justify the unusual form of intervention, such distinctiveness being the high “social cost of a bad drug brought to market.” But, Morton and Kyle do not spell out why the potential for such an unfortunate event means that the several aspects of pre-market approval beyond “provision of information about a product’s quality from a trusted third party” are desirable.

In his famous article “The Market for ‘Lemons’: Quality Uncertainty and the Market Mechanism,” George Akerlof explains the nature of the “lemons” problem:

There are many markets in which buyers use some market statistic to judge the quality of prospective purchases. In this case there is incentive for sellers to market poor quality merchandise, since the returns for good quality accrue mainly to the entire group whose statistic is affected rather than to the individual seller. As a result there tends to be a reduction in the average quality of goods and also in the size of the market. It should also be perceived that in these markets social and private returns differ, and therefore, in some cases, governmental intervention may increase the welfare of all parties. Or private institutions may arise to take advantage of the potential increases in welfare which can accrue to all parties. By nature, however, these institutions are nonatomistic, and therefore concentrations of power—with ill consequences of their own—can develop. (Akerlof 1970, 488)

Akerlof lists four “counteracting institutions” that can mitigate the lemons problem, three of which are potentially relevant to pharmaceuticals:

Numerous institutions arise to counteract the effects of quality uncertainty. One obvious institution is guarantees. Most consumer durables carry guarantees to ensure the buyer of some normal expected quality. One natural result of our model is that the risk is borne by the seller rather than by the buyer.

A second example of an institution which counteracts the effects of quality uncertainty is the brand-name good. Brand names not only indicate quality but also give the consumer a means of retaliation if the quality does not meet expectations. For the consumer will then curtail future purchases. Often too, new products are associated with old brand names. This ensures the prospective consumer of the quality of the product. ...

Licensing practices also reduce quality uncertainty. For instance, there is the licensing of doctors, lawyers, and barbers. Most skilled labor carries some certification indicating the attainment of certain levels of proficiency. The high school diploma, the baccalaureate degree, the Ph.D., even the Nobel Prize, to some degree, serve this function of

certification. And education and labor markets themselves have their own “brand names.” (Akerlof 1970, 499-500)

An invocation of Akerlof (1970) thus suggests certain immediate questions: Has there been or could there be “a reduction in the average quality of goods and also in the size of the market” because of doctor or patient reliance on one or more “market statistics”? What, if any, market statistic or statistics are used by the would-be consumers of pharmaceuticals? And what counteracting institutions, if any, are functioning with regard to pharmaceuticals? Morton and Kyle (2011) do not directly address these three questions, but one can imagine some possible answers. For example, one set of possible answers to the latter two questions might be: Patients trust physicians to prescribe drugs, patients use some sort of vague sense about the average benefit of visiting a physician as a market statistic, and a counteracting institution is licensing of physicians. Another set might be: Patients and doctors use some sort of vague sense about the safety and efficacy of an ‘average pill’ as a market statistic, and a counteracting institution is manufacturer brand names. Both of these sets of answers seem somewhat absurd, but they suffice to illustrate how a pre-market approval skeptic might doubt that it is reasonable to proceed, from the notion that pharmaceuticals are a “credence good,” with no or little further elaboration to the specific remedy of pre-market approval.

Morton and Kyle provide interesting discussions of how pre-market approval often provides only small assurance of safety and efficacy because of the limitations of

clinical trials. They remark in particular that “relatively few drugs have been tested in children, so a great many pediatric prescriptions are off-label.” Later, they proceed to note that: “Subgroups of the population may benefit more or less from an approved drug.” But the reader is left the task of drawing out the implication that subgroups of the population may benefit from drugs that, on the basis of the clinical trials that have been done, remain unapproved. Why not let those be prescribed, at the very least to adults, by the same doctors who are already empowered to prescribe drugs “off-label” to children?

Marc Law (2004; 2011)

In an encyclopedia entry titled “History of Food and Drug Regulation in the United States,” Law provides this basis for such regulation:

Perhaps the most enduring problem in the food and drug industry has been the issue of “adulteration”—the cheapening of products through the addition of impure or inferior ingredients. Since ancient times, producers of food and drug products have attempted to alter their wares in an effort to obtain dear prices for cheaper goods. For instance, water has often been added to wine, the cream skimmed from milk, and chalk added to bread. Hence, regulations governing what could or could not

be added to food and drug products have been very common, as have regulations that require the use of official weights and measures. Because the adulteration of food and drugs may pose both economic and health risks to consumers, the stated public interest motivation for food and drug regulation has generally been to protect consumers from fraudulent and/or unsafe food and drug products.

From an economic perspective, regulations like these may be justified in markets where producers know more about product quality than consumers. As Akerlof (1970) demonstrates, when consumers have less information about product quality than producers, lower quality products (which are generally cheaper to produce) may drive out higher quality products. Asymmetric information about product quality may thus result in lower quality products—the so-called “lemons”—dominating the market. To the extent that regulators are better informed about quality than consumers, regulation that punishes firms that cheat on quality or that requires firms to disclose information about product quality can improve efficiency. Thus, regulations governing what can or cannot be added to products, how products are labeled, and whether certain products can be safely sold to consumers, can be justified in the public interest if consumers do not possess the information to accurately discern these aspects of product quality on their own. Regulations that solve the asymmetric information problem benefit consumers who

desire better information about product quality, as well as producers of higher quality products, who desire to segment the market for their wares.

For certain products, it may be relatively easy for consumers to know whether or not they have been deceived into purchasing a low quality product after consuming it. For such goods, sometimes called “experience goods,” market mechanisms like branding or repeat purchase may be adequate to solve the asymmetric information problem. Consumers can “punish” firms that cheat on quality by taking their business elsewhere (Klein and Leffler 1981). Hence, as long as consumers are able to identify whether or not they have been cheated, regulation may not be needed to solve the asymmetric information problem. However, for those products where quality is not easily ascertained by consumers even after consuming the product, market mechanisms are unlikely to be adequate since it is impossible for consumers to punish cheaters if they cannot determine whether or not they have in fact been cheated (Darby and Karni 1973; McCluskey 2000). For such “credence goods,” market mechanisms may therefore be insufficient to ensure that the right level of quality is delivered. Like all goods, food and drugs are multidimensional in terms of product quality. Some dimensions of quality (for instance, flavor or texture) are experience goods because they can be easily determined upon

consumption. Other dimensions (for instance, the ingredients contained in certain foods, the caloric content of foods, whether or not an item is “organic,” or the therapeutic merits of medicines) are better characterized as credence goods since it may not be obvious to even a sophisticated consumer whether or not he has been cheated. Hence, there are a priori reasons to believe that market forces will not be adequate to solve the asymmetric information problem that plagues many dimensions of food and drug quality. (Law 2004)

Law (2004) offers a more detailed explanation of credence goods than did Morton and Kyle (2011), but he connects such goods only to a need for “regulation” in general, not to the specific intervention of pre-market approval. When discussing the justification of regulation, Law speaks of “consumers” rather than of doctors and patients separately. A patient has the “experience” of consuming the good, but in the pharmaceutical market it is predominantly doctors who select and prescribe drugs, yet Law’s discussion carries forward as though patients decide and that prescription requirements—a status quo intervention addressed to concerns about patient knowledge—are somehow not relevant. None of the four citations Law provides in this section are to research on pharmaceutical markets, much less contain any empirical findings with regard to the existence or magnitude of the the purported problems.

In a later reference work, Law wrote:

The key public interest rationale for regulation of food and drugs is to solve problems of asymmetric information about product quality. One of the conditions required for markets to allocate resources efficiently is that buyers and sellers be equally well informed about the various dimensions of product quality and safety. If buyers have less information than sellers about the safety or quality of products (a situation known as asymmetric information), unregulated market outcomes may be inefficient. As demonstrated by economist George Akerlof, asymmetric information can give rise to a “market for lemons,” in which low-quality products drive high-quality products out of the market. The enforcement of laws that directly regulate product quality, or that require producers to disclose accurate information about product quality, can potentially improve the efficiency of market outcomes in situations of asymmetric information.

With respect to food and drugs, asymmetric information problems are pervasive. Are food and drug products really what they claim to be? For instance, is the “pure” maple syrup sold in the grocery store really “pure”? Throughout history, the problem of food and drugs adulteration (the cheapening of products through the addition of impurities) has been pervasive. Are food and drug products safe? Will a particular medicine actually treat the disease or symptoms it claims to

remedy? These are all questions about which buyers are likely to be less informed than sellers on issues of product safety and quality. On such issues, however, regulators can play a role in improving market outcomes. Laws requiring proper labeling of food and drugs can curb the first concern. Regulations requiring pharmaceutical manufacturers to test new drugs and establish safety and efficacy before they are marketed can alleviate the second. The judicious use of regulation may therefore have an important role to play in reducing informational asymmetries. (Law 2011, 126)

One of the effects of pre-market approval certainly might be to help a consumer answer the question “Will a particular medicine actually treat the disease or symptoms it claims to remedy?” As I have often pointed out above, less drastic interventions could also have that effect.

Daniel Carpenter (2010; 2009c); Daniel Carpenter, Justin Grimmer, and Eric Lomazoff (2010)

Carpenter is a professor of government who for some years has conducted research that he calls “The Harvard Project on U.S. Pharmaceutical Regulation.”⁶⁵ While Carpenter’s support for pre-market approval is discernible throughout this body of work, he has sometimes argued openly for the policy. In the centerpiece of his project, a lengthy study of the Food and Drug Administration titled *Reputation and Power* (2010), Carpenter states his views in the book’s final five paragraphs:

Should a government agency, in a democratic republic—one governed by a constitution and the rule of law—have these powers? A more compelling answer to this question demands a separate, still empirical but more philosophical inquiry. I believe, however, that a pharmaceutical regulator should carry directive, gatekeeping, and conceptual powers, limited of course by constitutional and legal constraints and, perhaps most important, by the politics of organizational reputation itself. In the modern pharmaceutical world, the sponsors and producers of medicine are powerful entities, rendered all the more powerful by political and economic transformations of the past

⁶⁵ Carpenter’s website for his project is <http://people.hmdc.harvard.edu/~dcarpent/fdaproject.html>.

century. The multifaceted regulatory power of the Administration, its gatekeeping authority, and the harsher faces and moments of its image, allow a miniature agency to check and constrain a very large and politically dominant industrial sector.

The Administration's gatekeeping power enacts a system of incentives that induces the production of far more information (and higher quality information) from drug companies and medical researchers than would otherwise have occurred. The FDA's power is essentially the capacity to demand of market aspirants that they test their drug in a setting which they do not entirely control, that they take 100, or 1,000, or 10,000 patients, flip a coin and assign research subjects to their treatment or a control group based on chance alone. The production of such information in large quantities provides a vast public good, one useful at once for those who will utilize the therapy and for those who will not, one beneficial for those who prescribe drugs and those who bear the costs of drug utilization, and a stock of information helpful for those who will develop therapies of the future.

The conceptual face of regulatory power may seem insidious, but it allows for the standardization necessary to scientific progress. Medical research and intellectual advancement depend upon a minimally common vocabulary, a set of terms that can be assumed for the sake of devoting cognition and effort to other questions. By defining

the sorts of numbers that are debated in drug approval and utilization, and by laying out standards by which drugs are deemed equivalent to one another or distinct, the Administration renders a whole host of health decisions and economic exchanges much easier and more predictable.

There are risks, to be sure, in trusting this multidimensionality of power to a single organization. Yet the very source of this power—organizational image—has consistently served as a force in constraining the behavior and aspiration of the Administration. Whether in the cautionary voice of academic pharmacologists, in the American public’s fear of an unproven sleeping pill, or in the protests of oncologists or AIDS sufferers, the collected voices that constitute the Administration’s audiences restrained the agency and affected the thinking and, quite plausibly, the emotions of its officials. In many ways, this politics of reputation carries its own regrettable moments and inefficiencies. Yet for the Administration, as with many other agencies, the politics of reputation enacts another form of representation and constraint.

For those dedicated to constitutional politics and the best traditions of American government, the duality of reputation and regulatory power is both defensible and promising. Regulatory power in its directive, gatekeeping, and conceptual faces coheres well with the Federalists’ vision of “strong” government that was necessary for the

protection of liberty in its republican understanding. Alexander Hamilton and other republicans believed in the capacity of government to create and facilitate systems of economic exchange and scientific learning. Critical to these functions was the information that government bodies gathered, commanded, ordered, and provided. At its best, the power of the Food and Drug Administration in the pharmaceutical world reflects the aspirations of the progressive vision of the early twentieth century in which the agency was forged. It reflects not only the advancement of modern science, but the traditions and theories of republican government. For pharmaceuticals as for other realms of activity governed by the state, the central criterion of sound governance is not mass or breadth, but legitimated vigor. (Carpenter 2010, 751-752)

Here Carpenter's discourse fits easily within the broad ambit of market-failure argumentation. He makes two public-goods arguments for the FDA. The first argument, explicit in its invocation of a public-goods problem, says that unregulated drug producers will not generate enough (or good enough) information about new drugs; this argument is equivalent to arguments I addressed thoroughly in reaction to Kenneth Arrow's responses to the K&B questionnaire. The second argument says that government action is needed to provide scientists with a common vocabulary, to define the numbers that are debated, and to determine standards by which drugs may be deemed equivalent.

What evidence suggests that government standardization of terminology, debatable empirics, and equivalency standards yields a net improvement overall? Carpenter points to a single possible saving, that of scientists' time and energy, but he does not explore possible losses from such standardization, let alone attempt to account for its "total effect" (Coase 1960, 44). The most obvious possible loss is the failure to make whatever scientific advances would have resulted from successful contestation of existing terminologies, empirics, and standards.

I suspect that Carpenter might wish to object by claiming that the FDA does not and should not actually preclude such contestation. He might also wish to say that arguments over terminology, etc., do and should carry forward in the scientific journals, and the FDA should promulgate whatever terminology, etc., best promotes the cause of human betterment. However, elsewhere in *Reputation and Power*, Carpenter declared that the regulatory process *does* derail much important debate and discussion:

[T]he Administration's historical emphasis upon pre-market regulation serves to conceal many issues surrounding the safety of marketed drugs. This suppression of issues and information does not flow from a bureaucratic conspiracy of any sort, but from the way that the Administration's powers are defined and limited. So too, the definition of pharmaceutical politics in terms of "safety" and "efficacy" excludes other important questions from discussion—the heterogeneity of

individual responses to drug treatment, the therapeutic experience of millions of human subjects in ongoing human trials, the continued operation of placebo effects in markets for prescription pharmaceuticals, and the therapeutic implications of drug advertising and labeling.

A conceptual facet of regulatory power rests more quietly, but not less forcefully, in the capacity to shape patterns and terms of thought and learning. It is fair to say that the basic terms, standards, schedules, and rules of modern drug development have been fashioned by the Administration as much as by any other global entity. (Carpenter 2010, 16-17)

So, in short, Carpenter points out that FDA gatekeeping power causes “suppression of issues and information” and exclusion of “important questions from discussion” in the discourse on medicine, and his tone suggests that these consequences may be regrettable. He then proceeds directly into discussion of how FDA conceptual powers shape “patterns and terms of thought and learning,” fashioning “basic terms, standards, schedules, and rules of modern drug development”—consequences he later endorses by saying “the conceptual face of regulatory power...allows for the standardization necessary to scientific progress.”

I believe it is important to compare Carpenter’s discussion of the discourse on medicine, and specifically his welcoming of the circumscription of that discourse that

results from FDA wielding of conceptual powers, with the following passage in which Carpenter discusses the discourse *on pharmaceutical regulation*:

There are dozens of writings on U.S. pharmaceutical regulation, and there are many, many more on prescription drugs and the American and global pharmaceutical industries. Those efforts, while collectively fascinating and occasionally enriching, often portray an all-too-simple landscape. ...

... in the aggregate, and over the course of decades of American and global history, those stories fundamentally mislead. More compelling and accurate truths lie not merely in between these extremes, but on other dimensions of experience. Ignoring these dimensions, these narratives divert our attention from the ongoing politics of experimentation and therapy, from the small but crucial battles over interpretation of data, over the meaning of a patient's heart attack or stroke, over the design of a medical experiment, over the image of a government agency, over the precedent and emotion induced by a particular decision. Perhaps most of all, they divert our attention from a world of immense complexity, nuance, and ambiguity. (Carpenter 2010, 26-27)

So here Carpenter finds that, in the discourse on pharmaceutical regulation, some narratives rival to Carpenter's "mislead," ignore "dimensions of experience," and "divert our attention" from important matters. Carpenter's reaction, it would seem, is to attempt to supplant these crummy "all-too-simple" narratives. Carpenter wishes to direct the attention of participants in the discourse on pharmaceutical regulation to dimensions previously ignored. He wants those participants to behold "a world of immense complexity, nuance, and ambiguity."

But, following Carpenter's own logic, one could point out that focusing on more dimensions, and facing up to immense complexity and ambiguity, will prevent participants in the discourse on pharmaceutical regulation from "devoting cognition and effort to other questions." The judgments rendered on pharmaceutical regulation by those participants would actually be much "easier" and "more predictable" if their attention were diverted to portrayals of an "all-too-simple landscape." But would that be *better*?

Pharmaceutical regulation touches upon politics, law, medicine, science, business, and foreign affairs. In writing this book, I have incorporated methods and insights from many disciplines—history, pharmacology, political science, law, medicine, public health, mathematical finance and economics, sociology, mathematical statistics, and anthropology. (Carpenter 2010, 30)

Would any of these disciplines be improved if a regulatory agency wielding great conceptual powers were imposed upon it?

The world of pharmaceutical regulation is subtended by a vast number of trade reporters, newspaper reports, business and finance journals, science magazines, medical journals, and...“web logs” available on the Internet. (Carpenter 2010, 31)

Are we to believe that this “world of pharmaceutical regulation,” in which Carpenter is a prominent participant, gets along fine? If so, why are we to believe that the analogous ‘world of medicine,’ in which Carpenter is not a participant, struggles mightily?

How would professors of economics react to a proposal that conceptual powers over discourse on pharmaceutical regulation be wielded by a new agency of the U.S. government in order to reduce the expenditure of cognitive resources? How would they react to an argument that, by providing “a minimally common vocabulary” and “defining the sorts of numbers that are debated,” having such an agency would “allow the standardization necessary” to improve that discourse?

* * * * *

In a 2009 book chapter, Carpenter offers a fuller defense of pre-market approval, one that purports to transcend market-failure argumentation. In the opening paragraph he claims that “Effective regulation helps to maintain a structure of beliefs that make prosperity and liberty possible (or appreciably more likely). Regulation, in other words, in some sense creates the very possibility of marketplaces” (2009c, 164). He writes:

Many theories of regulation start not with institutions but with an institutional vacuum (an unregulated market) and then proceed to deduce the set of market failures that would justify their creation. [... Such market failure thinking] presupposes...that societies could somehow generate vibrant markets in the absence of webs of supporting institutions.

In this treatment, then, I start with the regulatory institutions themselves, not as an add-on to the market but as a basic institution whose institutions need better understanding.

The institutions of pharmaceutical approval furnish a useful place to begin. Table 5.1 displays the year that twelve nation states and the European Union first created regulatory bodies for pharmaceuticals and the year in which those same bodies instituted a compulsory premarket approval process. (Carpenter 2009c, 166-167)

Carpenter suggests that regulation⁶⁶ molds expectations into a form that facilitates trade, though he obviously would grant that markets for pharmaceuticals existed before “regulatory bodies for pharmaceuticals” came along. His rhetorical declarations that regulation “creates the very possibility of marketplaces” or fills an “institutional vacuum” thus are counterproductive in the context of a discussion of pre-market approval. The question at issue is whether those particular regulatory bodies and specific policies lead to fortunate outcomes.

Carpenter writes that approval regulation—his term for a category of intervention that contains pre-market approval (see *supra* note 2)—“represents a case of strong state power, namely the veto capacity of a government agency over research and development, and the related requirement for private actors to engage in greater R&D than they would otherwise in order to gain marketing rights” (2009c, 165). But we don’t know how much R&D firms would do otherwise. Carpenter and Ting (2007) provide one model that

⁶⁶ Carpenter seems to use *regulation* in two senses, only one of which I find appropriate. His equation of “an institutional vacuum” with “an unregulated market” (Carpenter 2009c, 166) is at odds with common usage. An economist writing of an “unregulated market” for pharmaceuticals would be understood as invoking not formless anarchy but rather an ordinary institutional environment with customs, property, organizations, law, courts, police, etc., but devoid merely of those legal restrictions understood to be “regulatory.” For example, in a *Journal of Economic Perspectives* article on the FDA, Tomas Philipson and Eric Sun use “regulation” to denote oversight by the FDA *in addition to* product liability law, e.g., “A longstanding literature in economics considers whether and under what circumstances regulation can produce more efficient behavior than liability alone” (2008, 92). But usually Carpenter does hew to the economists’ definition, such as when he lists the dates on which several nations “first created regulatory bodies for pharmaceuticals” (2009c, 167) or traces “The Ambiguous Emergence of American Pharmaceutical Regulation, 1944–1961” (2010, 118-227).

purports to show greater R&D in the presence of approval regulation, but what the model really shows is greater R&D *on products that are approved*. Carpenter and Ting dismiss the reduction in R&D on deterred products by characterizing those products as “poor” (Carpenter 2009c, 180).

Carpenter (2009c, 165) proceeds to “advance four arguments” about approval regulation. The first, paraphrased, is that “republican polities” impose approval regulation, and they do not do so because of regulatory capture. Certainly republican polities can err.

Secondly, Carpenter argues that “institutions of entry and approval regulation have arisen in markets characterized by learning constraints, including credence good markets and markets with appreciable information asymmetries” (2009c, 165). But approval regulation is not imposed on all or even many such markets—indeed, I have claimed it is essentially *unique* to pharmaceuticals, and despite his rhetorical treatment of approval regulation as a category of intervention, Carpenter too provides only a single example of approval regulation: “The emblematic case...national pharmaceutical regulation” (ibid., 164).⁶⁷ It does make sense that “markets characterized by learning

⁶⁷ Posner and Weyl (2013, 1348) offer “the review of proposed mergers by the Department of Justice and the Federal Trade Commission” as an example of intervention similar to pre-market approval. Posner and Weyl proceed to say “it is clear that they [the FDA process and the merger-approval process] are exceptional. Most other products and commercial decisions in American society are not under such rigorous control: while the government may occasionally inspect for safety, test properties of products, and allow

constraints” are where problems and tragedies occur to which pre-market approval is the sort of plausible remedy that would appeal to politicians and voters. I also concur when Carpenter says later that our market-failure argumentation should not be confused with the actual reasons that the institutions arise. Just because a policy may be adopted in reaction to difficulties perceived as related to certain credence goods, does not mean it is a well chosen corrective to a market failure.

Elaborating his argument about credence goods, Carpenter (2009c, 174-178) summarizes a model from an earlier working paper (Carpenter 2005):

The upshot of these models is that otherwise rational consumers will, under placebo learning from diseases with self-remission or other forms of cyclicity, consistently overestimate the therapeutic effect of the treatments they try first. They will either fail to rationally abandon a bad medicine, or they will abandon the therapy eventually, but too slowly. This serves as a brute but effective metaphor for the continued profitability of quack treatments and methods in therapeutic markets, particularly unregulated and less regulated therapeutic markets. As shown in many historical examinations of the subject, the market for patent medicines in the United States was immensely profitable,

lawsuits if harms occur, pre-approval of new products is uncommon outside of medicine” (ibid., 1349). Posner and Weyl then argue that the financial industry is like the pharmaceutical industry in the ways that they believe justify pre-market approval.

especially among well-educated and literate sectors of the population. Although it is far short of an empirical demonstration of the theory, it is worth noting that similar patterns hold for many nutritional supplements today. The enduring marketing strategies pursued by the purveyors of health scams further bear out these theoretical ruminations, dependent as they often are on heartfelt personal testimonials.

Theoretically, it is but a brief step from these results—which essentially endogenize the credence good properties of drugs and other therapeutic commodities (that is, explained through assumptions internal to the nature of those goods)—to the analyses of Akerlof (1970) and Leland (1979). When consumers consistently choose inferior products, then cheaply developed bad products drive out good alternatives, and the induced distribution of product quality is less than would be the case in the absence of placebo- and remission-based learning constraints.

Speaking more practically, learning constraints in therapeutic markets generate at least two additional thorny problems. First, therapeutic sponsors no longer invest in areas where the bad drugs take up space. This is the Akerlof “crowd out” hypothesis, and it is directly testable in the pharmaceutical arena. Second, consumers (patients) get stuck on the bad drugs and suffer worse health outcomes. Evidence for this claim comes from Jishnu Das’s study of the market for physicians in India (2001).

A more detailed logic of this model essentially elaborates upon the difficulty of decentralized, market-based learning about efficacy. When medical conditions are either self-remitting or cyclic (following a natural history), the impact of placebo effects upon human learning is multiplied. Such situations frustrate decentralized learning about product quality in therapeutic markets; even markets characterized by many consumers and many products will end up with long-term (asymptotic) bias. In other words, no matter how many people take the products, and no matter how long they take them, the true quality of the products will never be accurately revealed to anyone, much less to the whole of society. ...

From this point the standard “lemons” arguments of Akerlof and others apply. Either uncertain consumers will not sign up for the pharmaceutical “lottery” and will forgo superior treatments that would have been good for them, or they will continually choose inferior treatments that will drive more expensive and superior alternatives out of the market. (Carpenter 2009c, 176-178)

Carpenter offers here a “lemons” story that is more clearly specified than those told by Morton and Kyle (2011) and Law (2004). First, when discussing credence goods, Carpenter (2009c) explicitly equates consumers with patients, which was only implicit in Law (2004). Second, Carpenter describes patients as facing a choice to “sign up for the

pharmaceutical ‘lottery’” based on their perception of the “distribution of product quality,” which is his answer to the question, unanswered by Morton and Kyle (2011), of how consumers are using a market statistic and thus potentially triggering the lemons problem. But, like Law, Carpenter does not discuss the role of physicians and the highly relevant status-quo intervention of prescription requirements. Ironically, Carpenter’s evidence that “consumers (patients) get stuck on the bad drugs” is a study of patients’ choices regarding *which doctors to patronize*. Jishnu Das (2001) examines health care in India, where “practitioners in the informal sector...are the dominant source of health provision in the country: in one out of every two cases, first contact is with such a practitioner. They are the largest segment of the health market with four providers for every doctor in the formal sector” (Das 2001, 3). Das questions what he sees as a high level of spending on the services of these practitioners, who deliver poor results. The prevalence of unregistered ‘medical practitioners’ in India obviously is the result of a myriad of causes, which is one reason the situation does not offer a strong analogy for the consumer choice problem in pharmaceuticals in the United States, especially considering that the latter is mediated through physicians via prescription requirements. But assuming for the moment that it were a good analogy: If India were consistently enforcing a requirement that patients could only patronize a given practitioner after obtaining a specific recommendation from a licensed expert, would that resolve the problem? It might or might not, but it is certainly the kind of remedy that comes to mind. In the analogy to the U.S. market for pharmaceuticals, prescription requirements would be that kind of remedy. Yet in Carpenter’s section on the “Credence Goods” rationale for

approval regulation (2009c, 173-178), there is no acknowledgment that prescription drugs are already only available once the patient's "experience" is mediated through a doctor's judgment. When the problem on offer is that of patient learning, it is not clear why prescription requirements do not suffice.

Thirdly, Carpenter argues that "Institutions of approval regulation may serve to produce more information, and higher-quality information, than would be provided in their absence. By raising the returns to research and development, institutions of approval regulation also induce the production of superior and lower-variance commodities" (2009c, 166). Carpenter writes:

Approval regulation sharply truncates the array of products that the consumer faces. Speaking in mathematical concepts, if a consumer (the patient, or that patient's physician) is uncertain about a product, such that she faces a nondegenerate distribution of efficacy (a range of potential outcomes), then an entry restriction can be welfare improving if it dampens the "lower tail" of the distribution (or restricts the especially problematic cases). In even more precise mathematical language, entry regulation *must* induce a product quality distribution that first-order stochastically dominates the original distribution... Notice that this argument is about welfare; nothing about the preceding argument implies that regulation is efficient or the best way of obtaining

improvements in patient welfare. (Carpenter 2009c, 178-179, my emphasis)

Here Carpenter is relying again upon a model such as Carpenter and Ting (2007) that, as he acknowledges, is one of approval regulation *per se* and not a comparison against alternative remedies, such as direct efforts to reduce physician uncertainty. But he is incorrect in claiming that a thin model such as Carpenter and Ting's can sufficiently demonstrate that approval regulation "must" induce a superior product distribution (Carpenter 2009c, 179). This sort of model inevitably assumes that the processes determining firms' discoveries are the same whether there is approval regulation or not, but that is surely not the case. As Carpenter discusses elsewhere (2010, 16-17, 64-65), the R&D conducted under approval regulation is likely of a very different conceptual character than it might otherwise be. It must then be possible that the absence or presence of pre-market approval could cause, say, a 'fat tail' of fortunate or unfortunate drug discoveries.⁶⁸ Such an alteration in research paths might or might not swamp any effects of approval regulation when and if it "dampens the 'lower tail'."

Carpenter also writes:

⁶⁸ "Because of advances in science, we would expect productivity of R&D to change over time, thus making it difficult to predict current probabilities using old data. Moreover, success probabilities depend on which innovations are pursued, which are endogenous choices of the firm" (Morton and Kyle 2011, 779-780).

the requirement[s] for controlled studies of therapeutic products...brought forth a new commercial world. They created a 'scientific' demand for new instrumentation and new research capacity. More importantly, they generated a far broader and deeper demand for pharmaceutical goods, in part because of the way that government certification then triggered insurance coverage. A similar story can be told for the American market for 'generic' drugs, which took off only after the FDA and Congress established common standards for the 'bioequivalence' of generic drugs to the pioneer molecules they were trying to copy. (Carpenter 2009c, 181)

Carpenter asserts positive effects from required testing and standards-making efforts, but it would be very hard to untangle the many causes to which those effects could be ascribed, or even to gauge whether the effects were truly fortunate. Carpenter also leaves the extent of desirable testing unspecified, and testing could be required without banning products deemed to have low efficacy. More fundamentally, here he does not tell a story of redeemable market failure, but one of government entrepreneurial success. A story devoid of market failure gives us little sense of when government should refrain from acting. If political leaders acted today to stimulate "a far broader and deeper demand for pharmaceutical goods," would it be a good thing? Market failure rationales give us some reason to think demand is too high or too low.

Fourth, Carpenter writes that “The restrictions of institutions of approval regulation and entry regulation, combined with this information provision, can and often do materially improve human welfare in the setting of advanced republican polities, where the occasional drawbacks of these regulatory policies can be detected and reformed through legislation and other mechanisms of revision” (2009c, 166). He elaborates:

There are many dimensions on which one can compare institutions of approval regulation with other arrangements, but I am concerned here with three especially trenchant comparisons. First, effective approval regulations create a market with better products, in part through the direct effect of screening, in part through by [*sic*] indirectly encouraging private abandonment and “crowd out” of quack products. Second, even if the characteristics of the products in the market do not change, approval regulation may generate better information about the products that exist. Third, in a particular way, approval regulation may protect a vital form of liberty, emancipating citizens from unjust subjection to the whims and capricious decisions of producers. (Carpenter 2009c, 181)

Of these three comparisons, the first is another reiteration of the claims of, e.g., Carpenter and Ting (2007). Carpenter does not strongly defend the second comparison, about fortunate informational effects from approval regulation, terming it just “plausible

(though perhaps hard to assess empirically)” (Carpenter 2009c, 184); I consider this matter above when discussing Arrow’s response to the K&B questionnaire. With regard to the third comparison, the matter of “liberty,” Carpenter explains:

The underlying mechanisms linking approval regulation to liberty have at least two dimensions. By reducing the ability of producers to defraud consumers, approval regulation dramatically improves the capacity of individuals to make informed decisions about crucial dimensions of their lives. ... In addition, by constraining the ability of powerful producers unilaterally to set the terms of market interactions (as in antitrust), institutions of approval regulation may serve as a countervailing force to concentrations of economic power. (Carpenter 2009c, 184-185)

Carpenter thus characterizes approval regulation as having ameliorative effects against fraud and monopoly, but he does not explain why the existing laws against fraud and monopoly (such as antitrust) do not or cannot deliver such positive effects in a more targeted fashion. In a footnote at the end of the paragraph, Carpenter allows that some of his argument is “rather opaque” (2009c, 185 n.16).

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In joint work with Justin Grimmer and Eric Lomazoff, Carpenter has pursued further the idea that approval regulation increases consumer confidence. Carpenter, Grimmer, and Lomazoff propose a model yielding a second-order knowledge effect that they say should be incorporated in “contemporary cost-benefit analyses” of approval regulation (2010, 383). But nowhere do Carpenter, Grimmer, and Lomazoff cite any such cost-benefit analyses, surely because hardly any such analyses have been done (*supra* note 4); the only empirical studies that Carpenter, Grimmer, and Lomazoff mention are ones that they readily admit are not studies of approval regulation (2010, 397-398).

When addressing the notion of confidence effects of pre-market approval above (in response to Don Husereau), I offered three doubts: “it is very unclear that pre-market approval is the best means by which confidence in medicine might be increased, nor is it clear how such confidence-boosting efforts could be calibrated so as not to overshoot the mark, nor how analysts are supposed to locate that mark in the first place.” Carpenter, Grimmer, and Lomazoff (2010, 401-402) speak to the first doubt, contemplating “whether a market-entry veto is a necessary or an optimal way of achieving the confidence benefits of safety regulation” without drawing a definite conclusion. But they do not speak to the second or third doubts at all, though they do acknowledge the possibility of overconfidence:

One might also worry that approval regulation for consumer financial products would induce consumers to be too friendly to new mortgages,

loans, and other instruments. To be precise, this is not a problem with our model per se, as it renders a more compact prediction—not so much that consumption in general will increase, but that consumers will switch more readily to products that are in fact superior for them. Yet in general, it is a plausible worry that a regulatory floor may induce behaviorally limited consumers to attach too much faith to new financial products. (Carpenter, Grimmer, and Lomazoff 2010, 399-400)

Given that pre-market approval exists today and similar regulation of financial products does not, the consequences when consumers “attach too much faith” to new *pharmaceutical* products are more important to consider—and such consequences, of course, are potentially terrible. Carpenter and collaborators affirm that this is a potential result of pre-market approval and a “plausible worry.” Also, it is sometimes claimed that consumer confidence in medical interventions may already be too high (see, e.g., Angell 2004, 169-170; Brownlee 2008, 5-6, 9-10; Hoffmann and Del Mar 2015). Wisely, Carpenter and collaborators do not definitively affirm the status quo with regard to consumer confidence in pharmaceuticals or argue that it should be augmented further, but rather conclude that the matter deserves study.

Uwe Reinhardt (2007)

In a book chapter titled “The Pharmaceutical Sector in Health Care,” Reinhardt offers this explanation of pharmaceutical regulation:

One could imagine a world in which pharmaceutical companies could develop, produce, and market their products without any government supervision whatsoever. ...

In practice, no country follows that libertarian approach. Apparently reliance on private market forces and litigation as adequate safeguards in pharmaceutical therapy is viewed as much too risky. First, the protection of limited liability granted the owners of publicly traded companies severely limits the recourse injured parties would have to the personal wealth of the owners of pharmaceutical companies. The now universal principle of limited liability allows the owners of an enterprise to escape most of the financial consequences of even truly grievous mischief that a company may have visited on behalf of these owners on the rest of society, including grievous environmental hazard. Many corporate executives may not be aware that this protection actually is one of the earliest forms of social insurance. Second, no country is willing to countenance the human casualties that this approach to product safety would have. Although, using a human capital approach,

economists probably could justify these casualties in many instances by the added lives saved, the general public and the politicians who represent them undoubtedly would not find the economists' collectivist calculus persuasive.

It may well be that the public authorities who do attempt to safeguard the quality of pharmaceutical therapy in each country, for example, the U.S. Food and Drug Administration (FDA) in the United States, typically may be more averse to risk, and hence more restrictive, than would be the majority of the patients being protected. Even so, on balance, both the general public and the pharmaceutical industry probable [*sic*] benefit greatly from the existence of these public authorities. Pharmaceutical companies benefit from having a powerful external stimulus for internal quality control. Furthermore, approval of a product by the authorities can serve as a helpful, if not decisive, shield in litigation over product safety. Few pharmaceutical companies around the globe would be likely to prefer a world without such public supervision. (Reinhardt 2007, 28-29)

Reinhardt first argues that limited liability “limits the recourse” of those injured by “grievous mischief” on the part of pharmaceutical companies, whose owners would “escape most of the financial consequences.” Can this work as a defense of pre-market approval? Most unfortunately, the example Reinhardt provides of such mischief is not

related to pharmaceuticals but is rather “grievous environmental hazard.” Pharmaceutical companies cannot unilaterally spill their product into patients’ bloodstreams, so the analogy does not well convey an argument for pre-market approval. Presumably the argument is that regulatory oversight heads off overt disasters. Reinhardt then proceeds to argue that even if such disasters were shown by economists to be redeemed by a greater number of lives saved—through the averting of what I will call a ‘statistical’ disaster—politicians and the public would reject the economists’ findings and persist in their preference for fewer overt disasters but more lives lost. Reinhardt concludes by arguing that regulation helps pharmaceutical companies by spurring them to produce safer products, and since those products will be approved by regulators, the companies will then be shielded from much litigation.

I think it is fair to claim that pre-market approval works to head off tragedies such as that of Elixir Sulfanilamide, a case in which a poison—known by many scientists as such—was used by an ignorant or erring chemist to reformulate a product in a rushed manner. Some form of approval regulation can work to head off that sort of tragedy by drawing a disconnected firm and its chemists into what one might call the ‘network of science’ and insisting that they submit to a check for mistakes. I think it is wrong to think that pre-market approval works to head off tragedies such as that of thalidomide or Vioxx if we conclude that, given the knowledge and practices of the times, review by the

‘network of science’ would have been insufficient to find the problems.⁶⁹ That is to say: There is a class of drug tragedies that will happen even under pre-market approval, and indeed, they could be exacerbated if regulator approval leads to greater consumption than there would be without the intervention. But, one can go further to ask: Are there remedies other than pre-market approval that can prevent the same tragedies that pre-market approval would head off? If we use Elixir Sulfanilamide as an exemplar of such a tragedy, then it would seem that a policy regime that does not insist on evidence of efficacy is sufficient. But we could imagine a different sort of tragedy, say, one in which a drug is consumed widely by patients who erroneously believe it to have large beneficial effects but who correctly apprehend its ‘safety’ risks; in this case evidence of a lack of efficacy would be valuable.

⁶⁹ It is debatable whether a required check for mistakes by the ‘network of science’ as it existed in 1960 would have prevented the thalidomide tragedy. The German producers of thalidomide were arguably only on the fringes of that network (Brynnner and Stephens 2001, 1-17), and the review of thalidomide by the FDA did successfully prevent its marketing in the United States. But the key factors that led to FDA to delay thalidomide’s entry were two: reputation-based skepticism of the U.S. licensee (the William S. Merrell Company), and reports of a different side effect (peripheral neuritis) that had become known because the drug was already being marketed in Europe (Brynnner and Stephens 2001, 39-55; Carpenter 2010, 217-226). So while perhaps the German firm should have known to check for teratogenic effects, if we take the FDA review as representative of the ‘network of science’ at the time there seems little to assure us that the teratogenic effects would have been caught. On the other hand, perhaps review by the ‘network of science’ should be presumed not to be dryly ‘scientific’ but rather presumed to inevitably incorporate or reflect reputational assessments. Then, if we take the FDA review as representative, we might conclude such a review had the potential to have prevented the thalidomide tragedy considering the skepticism that the FDA had of the U.S. licensee.

Ideal policy would head off both overt disasters *and* ‘statistical’ disasters. Reinhardt notes that overt disasters are politically intolerable, which suggests that when there is a direct tradeoff leaders will err on the side of avoiding the overt disaster. It also suggests that, when leaders err too far on that side, creating needless ‘statistical’ disasters that are detected by economists, the economists need to be as persuasive as they can manage.

Tomas Philipson and Eric Sun (2008)

A *Journal of Economic Perspectives* article by Tomas Philipson and Eric Sun (hereafter P&S) (2008) is notable for its explicit use of product liability law as the baseline against which the desirability of FDA regulation should be evaluated.

A longstanding literature in economics considers whether and under what circumstances regulation can produce more efficient behavior than liability alone. This literature bears on the analysis of FDA by seeking to explain why so many governments have sought to regulate the safety of medical products, as opposed to relying on product liability alone. Direct premarket regulation of safety may be desirable if product liability is in some way incomplete in providing the correct

level of deterrence to the production of unsafe products, which can occur for several reasons.

First, product liability will be an incomplete deterrent to the extent that firms can evade judgments through limited liability. For example, unsafe medical products can lead to very large losses among consumers, because health and life are valued highly. As a result, firms may be able to avoid judgment by declaring bankruptcy (Shavell, 1987). Moreover, when losses are large, firms have greater incentives to distort the liability system (by legal or illegal means) in a way that makes that system likely to deter less than it should—which is one explanation for the change from liability to regulation over time (Glaeser and Shleifer, 2003).

Second, with many medical products, it can be difficult to establish whether the firm is at fault, because patients who suffer serious losses from a given drug often have other cofactors which predispose them to injury. As a recent example, Merck, the maker of Vioxx, is being sued by patients because of the increased risk of heart attacks associated with Vioxx usage. However, many patients who used Vioxx has several other risk factors for heart attacks, therefore making it difficult for the jury to determine whether a given heart attack was caused by Vioxx itself. More generally, if consumers are imperfectly informed, then governments or a private third party may economize on the costs of verifying product quality.

Third, new medical products that are the focus of safety and efficacy interventions are provided by firms with patent protection and market power. As

we argue in Philipson and Sun (2007), in such cases safety may be underprovided by a monopolist under product liability for reasons related to underprovision of quality by monopolists more generally (Tirole, 1988).

Fourth, regulation is a fixed cost for each product, while litigation can involve costs proportional to the number of those potentially harmed, which makes regulation more favorable for larger economies and populations (Mulligan and Shleifer, 2005). (Philipson and Sun 2008, 92-93)

First, P&S argue that regulation may be necessary because drug firms can evade liability by declaring bankruptcy. Is pre-market approval the best remedy? P&S do not consider alternatives. If the concern is compensation for those injured when injuries occur, a directly relevant remedial intervention could be to require drug firms to carry insurance. Or, if the concern is reduction of injuries, then we are simply speaking about which system is safer. With regard to the argument about distorting the liability system: The present value of a drug approval might be similar (or greater) in magnitude to potential damages from a court case, and thus firms may well have comparable incentive to distort the pre-market approval system.

Second, P&S argue that it is hard for a jury to assign definite fault in a drug-safety case. P&S suggest that drug hazards are best assessed in a population of users, because in any single case they will interact with the individual patient's peculiar susceptibilities. Since the same drug could potentially be involved in a variety of cases, it is more

economical for there to be one, more deliberate assessment of the drug than to have assessments by many separate juries. Is this more than the ordinary idea behind class-action lawsuits? Furthermore, lawsuits today are filed on behalf of those harmed by *approved* drugs, so it is not clear how this argument could be used to justify the particular regulation of pre-market approval, where many drug hazards are not identified until the drug is widely used. I sense rather that P&S believe this is an argument for a reform such as preemption (see Philipson, Sun, and Goldman 2010).

Third, P&S argue that drug producers, being firms with market power, will underprovide quality. Again, the relevance of this supposed market failure to the specific remedy of pre-market approval is hard to ascertain. First, direct interventions come to mind such as patent reform and antitrust action. Second, if we are speaking of market power as caused by “patent protection,” which P&S seem to be doing, it becomes tricky to explain in what sense quality is underprovided *because* of market power. The patent is a patent on a molecule, and the molecule is what it is. Other firms’ opportunities to develop molecules of ‘higher quality’ are not diminished by the patent. There is no way to ‘cut corners’ and thus ‘underprovide quality’ of a molecule. There are of course ways to cut corners in the manufacturing of pills or injectables, but that form of quality assurance is not at issue.

Fourth, P&S argue that regulation will be a cheaper means than litigation of achieving the desired ends. But their evidence is only the assertion that “regulation is a

fixed cost for each product,” an assertion that finds no support in the article cited by P&S. Casey Mulligan and Andrei Shleifer (2005) develop a model in which they “assume that regulation requires a fixed cost *of adoption and administration* and derive the equilibrium quantity of regulation in a community as a function of its population, and *fixed and variable costs*, as well as the benefits, of regulation” (Mulligan and Shleifer 2005, 1447, emphases mine). Mulligan and Shleifer do not address pharmaceutical regulation at all, much less the question of whether the adoption of pre-market approval has been appropriately adopted in light of its costs and benefits.

Generally, as shown above, P&S fail to discuss different forms of remedial intervention. Their discussion almost seems to equate “regulation” with “direct premarket regulation of safety.” Furthermore, their analytical energies here are focused on product liability, with regulation subjected to little analysis; for example, pre-market approval is treated as if it unerringly ascertains safety.

Anup Malani and Tomas Philipson (2012)

Malani and Philipson (hereafter M&P) set aside nine pages of their handbook chapter “The Regulation of Medical Products” for a section titled “Rationale for

Government Regulation” (2012, 106-115). The section’s introductory paragraph divides “FDA regulation of medical products [into] two basic components.”

The first is production and dissemination of information and analysis about quality of drugs and devices. This is embodied in the FDA’s requirements that companies produce data to demonstrate safety and efficacy and that drug and device labels report indications as well as contraindications and adverse effects. The second is a minimum quality regulation. This is directly embodied in the FDA’s rule that drugs and certain devices cannot be sold until they have been demonstrated to be safe and effective. (Malani and Philipson 2012, 106)

Most of the section is given over to the sketching of formal frameworks that could be used to illustrate the size of certain welfare gains and losses presumed to come from regulation. In a preceding subsection, “Minimum Quality Standards,” M&P give market-failure rationales for that central component of FDA regulation:

There are two basic ways to justify the government’s imposition of these minimum quality standards on consumers who would use their own money to pay for products. First, even if the government provides information that a product is not safe or effective, a consumer may still consume it because there is a cost to processing information from the

government. This lost value need not be bounded by the individual's cost of processing information. Because consumers do not know the value of the information from the government, they might not pay the cost of processing it even if, in hindsight, the value of processing that information would exceed the cost of doing so. A second justification for minimum quality standards is that individuals are unaware of their best interests and—importantly—are unaware that they are unaware. Therefore simple paternalism may justify FDA screening. (Malani and Philipson 2012, 110)

M&P (2012), again, is a chapter titled “The Regulation of Medical Products.” But the chapter never refers to prescription requirements, viz., the distinction between prescription drugs and over-the-counter drugs. Only in a footnote do M&P make any use of the idea that doctors are presently charged with choosing drugs from the universe of approved drugs (*ibid.*, 106 n.6). In the presence of prescription requirements and doctors charged with choosing among approved drugs, M&P's argument for minimum quality standards—that “consumers do not know the value of information from the government,” and because it is therefore possible that consumers will undervalue that information and then decline to obtain and process it—is, essentially, equivalent to the argument that knowledge is too expensive to communicate to doctors, attributed to Arrow above. Arrow had said that doctors do not systematically err in prescribing; Malani and Philipson do not address the question of systematic error directly but suggest that “perhaps patients (and

doctors they might hire to help them) have cognitive limitations” (ibid., 106). I wrote above: “Doctors are provided with all manner of information about the universe of approved drugs, and we rely on them to process that information sufficiently to select drugs from that universe. What is the supposed difficulty that would be encountered in offering to doctors information about a larger universe of drugs?”

M&P present one other argument they say can justify minimum quality standards, the single sentence that “individuals are unaware of their best interests and...are unaware that they are unaware.” They provide no evidence that this is the case, nor that the government is more aware of individuals’ best interests, nor acknowledge that this line of argument could justify many conceivable economic interventions.

Both possible justifications of minimum quality standards, then, are based on the government’s superior assessment of information: either the government correctly values the information while consumers mistakenly undervalue the information, or the government correctly identifies consumers’ best interests while consumers misidentify their own interests. Whether there *are* benefits to the regulation hinges on one of these justifications being valid. M&P do acknowledge the possibility that the FDA’s judgment may not be superior and may even be inferior, but only briefly and without references:

An alternative to testing by the producer is testing by a third private party or the government. One concern with permitting medical product

companies to test their own products is that their studies may be biased in favor of their products. ... [G]overnment studies may have a bias toward finding that drugs have side effects. Indeed, the FDA has been criticized for being overly cautious with drugs, because although the agency is not given credit for new effective drugs, it is blamed when it permits an unsafe drug to enter the market. (To be fair, the FDA has also been criticized for being captured by the drug industry.) (Malani and Philipson 2012, 107)

They then drop these concerns and proceed under the assumption of a beneficial impact on knowledge from FDA regulation:

Whereas efficient and fair production of information is important, the central concern with the government's decision to produce information is whether the *benefits* of that information are worth the costs. (Malani and Philipson 2012, 107, my emphasis)

M&P's question has become: Do these benefits of regulation exceed the costs? They proceed to state: "If minimum quality standards are justified on efficiency grounds [meaning, their first argument] as opposed to paternalistic grounds [the second], we can evaluate these standards using the same graphs we used to illustrate the value of information from the FDA," and they add in a note: "When consumers are unaware of

their best interest [as in the paternalism argument] (i.e., utility), their prior demand curves are not an appropriate baseline from which to calculate the benefits of a change in demand after the production and processing of new information” (2012, 111, 111 n.12). So, just as the existence of benefits in their framework is determined by whether the FDA’s judgment is superior, so is the *size* of those benefits determined by the *magnitude of the superiority* of the FDA’s judgment as compared to consumers’ judgment—because that determines how far M&P’s demand curves will shift: “An important lesson from [the supply and demand charts in] panels C and D is that welfare effects of minimum quality standards increase according to the extent to which information increases welfare” (ibid., 111, regarding their Figure 5.2 on 109; see also 115 n.19).⁷⁰ But M&P find, in reviewing the literature, that there is almost no empirical evidence related to this question. They present a large number of studies trying to measure various costs of FDA regulation (ibid., 115-129), but only a single study—Peltzman (1973)—that tries to estimate effects on consumer demand of the provision of superior information.

M&P then excoriate Peltzman for supposedly failing to recognize that “information from the FDA increases consumer surplus by revealing the true demand for drugs”:

⁷⁰ M&P also offer a model incorporating two benefits of “more stringent minimum quality regulation” that are not related to their market-failure justifications: “the research expenditures avoided because of the reduction in innovation” and “the larger consumer surplus due to the additional time a drug may be marketed before it is withdrawn” (Malani and Philipson 2012, 114).

Peltzman (1973) claimed to address this issue but basically assumed it away. He supposed that, before the 1962 Amendments, consumers learned true demand from experience with a drug, so that even pre-1962 demand is true demand. Therefore, when Peltzman estimated a reduction in demand after 1962, he concluded that FDA regulation strictly reduced surplus. If pre-1962 demand was distorted by imperfect information, however, then his welfare estimates are incorrect. (Malani and Philipson 2012, 130)

If Peltzman (1973) is badly flawed, then per M&P's literature review there has been no useful empirical work done on the size of the benefits from pre-market approval. But while Peltzman's framework and findings can of course be disputed, the specific charges brought by M&P (2012) are I think overstated. In one of his empirical strategies, Peltzman assumes that some initial demand for pre-1962 new chemical entities (NCEs) was not "true" and that all initial demand for post-1962 NCEs was "true." He finds using that strategy "the estimated waste [for pre-1962 NCEs in the first year after introduction is]...\$0.4 million" (Peltzman 1973, 1077). For another empirical strategy Peltzman assumes that drugs deemed "not effective" by the American Medical Association "have no therapeutic value, so all consumer expenditures on them are pure waste" (ibid., 1084).⁷¹

⁷¹ Cf. the separate, yet tonally similar, criticism of Peltzman's analysis offered by Thomas (1990, 502, my emphasis): "Peltzman (1973) *suggested* regarding all changes in

Patricia Danzon (2011); Patricia Danzon and Eric Keuffel (2014)

In a handbook chapter, “The Economics of the Biopharmaceutical Industry,”

Danzon writes:

Although the biopharmaceutical industry is heavily regulated, the economic rationale for regulation is not structural barriers to competition. Rather, market access regulation is a response to imperfect and/or asymmetric information of consumers and physicians in evaluating the safety and efficacy of new products. ... Both positive and normative analysis of product differentiation and pricing must take into account heterogeneity in patients’ response to different drugs, and the roles of physician prescribing and third party payment as key determinants of demand elasticities. In this context, drawing welfare

premarket testing and other innovation costs after 1962 as entirely due to increased regulatory intensity.” Peltzman did *conclude* such, and his thought process or model for reaching that conclusion may fairly be faulted, but he explicitly considered the possibility that changes in “the cost of producing drug formulas” could be driven by rising “labor expense for R & D personnel,” and he then proceeded to observe there was “no upward trend or post-1962 increase in the relative wages of R & D and production personnel” (Peltzman 1973, 1053).

conclusions about optimal levels of R&D and product variety is complex. (Danzon 2011, 522)

The economic rationale for requiring pre-market proof of safety is that manufacturers may face suboptimal incentives to provide risk information to consumers in the absence of regulatory requirements. The requirement for pre-market proof of efficacy has been more controversial, given the high cost and launch delays associated with doing large Phase III trials required to establish efficacy and/or detect remote risks in subpopulations. The economic rationale for efficacy requirements is that imperfect information may prevent physicians and consumers from making accurate evaluations, leading to wasted expenditures on ineffective drugs and other associated costs, and possibly excessive product differentiation that undermines price competition. Firms may have incentives to exaggerate benefits and downplay risks in their promotion, given the high price-marginal cost margins. Moreover, setting standards and evaluating clinical trial evidence of efficacy and safety requires expertise and is a public good that can arguably be provided most efficiently by a single expert agency. (Danzon 2011, 523)

Some have argued that consumers should be permitted to make their own evaluations of risks vs. benefits based on phase II trials (Madden 2004). However, phase II trials are small, designed to provide proof of concept and preliminary dose-ranging evidence of safety and efficacy in select patient subgroups. Such trials lack the statistical power to provide credible results for general decision-making. A specialized agency such as the FDA accumulates expertise and provides a public good in evaluating the evidence on safety and efficacy, including requiring that minimum standards and reasonable tradeoffs be met as a condition of launch. Such information would be under-provided in a free market regime and cannot be efficiently assessed from the personal experience of individual physicians or even health plans, both of which have more limited information and expertise than the FDA and may be imperfect agents, given their financial stakes, respectively, in prescribing and controlling drug spending.

The expanded range of drug therapy and growth of insurance coverage have increased the social benefit of having a regulatory agency review and establish minimum standards for marketed drugs. When consumers paid out-of-pocket and few drugs were available, the main benefit of a regulatory requirement of efficacy was to protect consumers from wastefully spending their own money on useless drugs. Given the expansion in number and complexity of drugs available, with many

consumers taking multiple prescriptions for chronic diseases, the information burden of staying informed and the potential cost of being misinformed have increased, as has the potential for adverse drug reactions and interactions. The growth of insurance coverage has also undermined individual consumer's [*sic*] financial incentives to avoid wasteful spending on drugs that are of low or only minor benefit. These trends increase the public good case for a regulatory agency such as the FDA to establish minimum standards of safety, efficacy, and quality as a condition of market access. ...

A related question is the optimal role of tort liability, given regulation. The FDA is an expert agency that relies on internal specialists and external advisory panels comprised of medical and statistical experts who review and evaluate comprehensive data on risks and benefits. Their decisions should in theory be better informed, more consistent across drugs and more able to balance societal risks and benefits than the untrained juries that decide tort claims. Moreover, tort claims focus on adverse outcome to an identified patient, who may have had competing medical and life-style risk factors, rather than average effects for patients at large. For example, if the FDA decided that a 1 percent risk of an adverse outcome from a drug was acceptable in view of its benefits, how does a jury decide whether an individual patient's adverse event is within this 1 percent, in which case the firm should not

be liable, or lies outside the 1 percent, in which case the drug may be less safe than expected and the firm should be liable? More generally, notions of a “defective product” under strict product liability or “negligent product design” in a negligence claim, are problematic when applied to drugs for which it may be prohibitively costly to identify patients at risk of adverse response. Unclear standards lead to erratic and unpredictable liability rulings, in which case incentives for safety are likely to be excessive (Craswell and Calfee 1986). Moreover, tort decisions made ex post, after a drug has been on the market, are at risk of applying new information retroactively, holding a firm liable for a rare adverse effect that only emerges after widespread or long-term use of the drug, which could not reasonably have been foreseen without undue costs and delay of pre-launch testing that would deprive other patients of access. However the Supreme Court recently struck down the claim of pre-emption, that the FDA’s regulatory approval protects companies against liability when the agency’s instructions are followed, because the FDA has not expressly been given pre-emption by Congress. (Danzon 2011, 527-528)

The primary justification Danzon outlines is essentially a version of the formulation that *the regulator is evidently excellent*. She emphasizes the FDA’s “expertise” and argues that its judgment, as a component of knowledge, can be a public

good. By directly contrasting the FDA against physicians and insurers she terms “imperfect agents,” Danzon implicitly puts forward the view that the FDA is uninterested or faces no conflicts, as did Arrow and Matuszewski in response to the K&B questionnaire.

Danzon also offers three secondary justifications. The first is that pre-market approval reduces the cognitive burden on consumers, but this does not explain why a mere certification cannot adequately serve the same function (see my discussion of Arrow’s claim that drug information is “difficult to...understand”). The second is that insurance coverage enhances the value of pre-market approval because the latter deters “wasteful spending on drugs that are of low or only minor benefit.” But insurance companies and Medicare can simply decide not to cover such drugs, and the FDA does not take costs into account into account when making its decisions, so pre-market approval would be a blunt tool to address that matter. Third, Danzon argues similarly to Philipson and Sun (2008) that having the FDA evaluate drugs should be more economical than having evaluations made by multiple juries in the court system; unlike Philipson and Sun, she explicitly says this is an argument for preemption reform. FDA evaluation of drugs is consistent not only with pre-market approval but also less extensive interventions such as mere certification.

Danzon has also written, in joint work with Eric Keuffel, a long book chapter on “Regulation of the Pharmaceutical-Biotechnology Industry.” The chapter contains this discussion of market failures:

The rationale for heavy regulation of pharmaceuticals is not intrinsic natural monopoly, since any market power enjoyed by individual products derives ultimately from government-granted patents. Rather, regulation of market access, manufacturing, and promotion arise because product efficacy and safety can be critical to patient health but are not immediately observable. Evaluating safety and efficacy as a condition of market access and monitoring manufacturing quality and promotion accuracy over the product life cycle are public goods that can in theory be efficiently provided by an expert agency such as the Food and Drug Administration (FDA). (Danzon and Keuffel 2014, 407)

Generally, the high cost per new drug approved reflects high costs of preclinical testing and human clinical trials, high failure rates, and the opportunity cost of capital tied up during the eight to twelve years of development. To some extent, this high and rising cost of R&D reflects regulations that exist in all industrialized countries, requiring that new compounds meet standards of safety, efficacy, and manufacturing quality as a condition of market access. The main initial focus of

regulation since the 1930s was safety, and this has reemerged recently as a critical issue. Since the 1960s most countries also require pre-approval evidence of efficacy, monitor manufacturing quality throughout the product life, and regulate promotion and advertising to physicians and consumers.

The economic rationale for these requirements derives from the fact that the risks and benefits of pharmaceuticals are nonobvious, can differ across patients, and can only be known from controlled studies in large patient populations. Gathering and evaluating such information is a public good, and a regulatory agency that has both medical and statistical expertise can more accurately and efficiently monitor and evaluate the evidence from clinical trials than can individual physicians or patients. However, regulation that requires extensive prelaunch clinical trial data on safety and efficacy increases the R&D costs incurred by firms, increases delay in launch of new medicines, and may reduce the number of drugs developed and the extent of competition. The size and duration of clinical trials required to detect remote risks or cumulative risks from long-term therapies can be large. The rising costs of R&D, combined with new technologies for evaluating information, have prompted recent initiatives to accelerate approvals and optimally integrate evidence from preapproval clinical trials with postapproval observational experience. In the United States, the statutory regulation

of pharmaceuticals through the FDA is in addition to—and uncoordinated with—the increasing level of indirect regulation through tort liability. Critical unresolved issues in market access regulation are: (1) how much information on risks and benefits should be required prior to launch; (2) what is the appropriate trade-off between benefits and risks, given that some risks are inevitable; and (3) what is the appropriate mix of pre- and postlaunch monitoring of risks, what methods should be used, and what is the appropriate mix of regulation by an expert agency (such as the FDA or an independent agency) and tort liability? (Danzon and Keuffel 2014, 409)

Unlike some other industries, regulation of the pharmaceutical industry has not diminished or undergone fundamental changes over recent decades, although focus of market access regulation has shifted between concerns for safety versus cost and delays, and the structure of price/reimbursement regulation has become more complex. The motivations for regulation of pharmaceuticals—imperfect and/or asymmetric information for market access regulation, patents, and insurance-related moral hazard for price/reimbursement regulation—remain and have, if anything, increased over time. These are summarized in Table 7.1. (Danzon and Keuffel 2014, 411)

[Reproduced as in original:] Table 7.1 Objectives and examples of regulation of the pharmaceutical industry

Rationale for regulation	Examples of regulation
Imperfect information about drug safety and efficacy	Market access requirements of safety, efficacy, and quality Regulation of promotion Tort liability
High fixed costs of R&D	Patents and regulation of generic entry Orphan Drug Act Accelerated approval measures
Insurance-induced moral hazard	Regulation of prices, reimbursement, profits, expenditure/revenues

(Danzon and Keuffel 2014, 412)

The presumption underlying the requirement for proof of efficacy was that imperfect and possibly asymmetric information prevented physicians and consumers from making accurate evaluations, leading to wasted expenditures on ineffective drugs and other associated costs, and excessive product differentiation that undermined price competition. Although Phase III trials, involving double-blinded, randomized, placebo-controlled trials in large patient populations, were initially intended to establish efficacy, over time these trial requirements have been expanded to detect remote risks and/or cumulative treatment risks of chronic medications. The size and duration of clinical trials, together with increased regulatory review time, added to delay in the launch of new drugs, leading to foregone benefits for consumers, shorter effective patent life, and foregone revenue for firms, albeit with the intent of

avoiding potentially larger costs for consumers. Moreover, since some regulatory costs are fixed, independent of potential market size, such regulation raises the expected revenue threshold required to break even on a new drug, leading to higher break-even prices, *ceteris paribus*, and fewer drugs, particularly drugs to treat rare diseases with small potential market size. (Danzon and Keuffel 2014, 413-414)

Danzon and Keuffel (2014), like Danzon (2011), emphasize that the FDA is “expert” and available to aid consumers in dealing with “imperfect and/or asymmetric information,” but they do not explain why doctors and patients would not place appropriate trust in the FDA’s evaluations, were the evaluations simply published. Danzon and Keuffel specify that the informational market failure comes about because “the risks and benefits of pharmaceuticals are nonobvious, can differ across patients, and can only be known from controlled studies in large patient populations.” They do not make clear the connection they intend between the fact that treatment effects “differ across patients” and a need for a one-size-fits-all approval policy. Also, quite often the benefits of pharmaceuticals *are* rather obvious, and correspondingly it is not true that they can “only” be known from controlled studies (see Healy 2012, 64-95). Of course it is true that many times the benefits are nonobvious (and much knowledge about them can be gained from clinical trials), and it is then in particular where there lurks danger from the possibility that patient and doctor trust in a drug will prove unwarranted. Pre-market approval potentially amplifies that trust—and so it makes sense that Danzon and Keuffel

evinced strong belief in the FDA's wisdom, for if the FDA were instead prone to misjudgment, excessive reliance on its evaluations could be unfortunate.

Eric Posner and Glen Weyl (2013)

In a law review article, Posner and Weyl propose "An FDA for Financial Innovation." After noting that pre-market approval is an "exceptional" instance of "rigorous control," they write:

The question thus arises why financial innovation is more like pharmaceutical innovation than like other products of the U.S. economy. There are a number of answers.

1. Subjective Preferences and Expertise.—The best medicine for an individual to take is not something highly idiosyncratic to that individual, conditional on her observable symptoms. While different individuals usually respond differently to different treatments, this reaction is usually as unpredictable to the individual as it is to the doctor treating her or to anyone else prior to the treatment being administered. Thus the key consideration in determining the appropriate medicine is usually the use of the medical community's expertise to determine the

objectively best treatment for the patient rather than the treatment that she subjectively prefers. Not only do individuals usually consult doctors about the best medicine; doctors usually base their opinions on centrally conducted research.

These features of the market for medicine contrast sharply with those of most consumer products. When shopping for TVs, computers, or books, individuals usually know far more about their tastes than any expert would be capable of learning in any reasonable period of time. This capability makes allowing individual choice and providing individuals with richly detailed information (rather than a blunt permission or prohibition) far more important in most product markets than in health. And it makes access to expert advice much more important in health than in other product markets. (Posner and Weyl 2013, 1349-1350)

Posner and Weyl write in the first paragraph under “Subjective Preferences and Expertise” as if the practice of medicine proceeds as follows: “the” drug is chosen—“usually” by doctors, who “usually base their opinions on centrally conducted research”—to be administered exactly one time, and its effects are permanent and cannot be reversed or superseded.⁷² This informal model of how drugs are used is almost a

⁷² In that one paragraph, Posner and Weyl (2013, 1349-1350) twice speak of “the best medicine,” and once each of “the treatment,” “the appropriate medicine,” and “the

mirror image of the formal model put forward by Carpenter (2009c, 174-178), in which *patients* initially pick a drug *essentially at random*, and then must decide on the basis of *their personal experience* whether to *continue* taking the drug or to switch. Whereas Carpenter's model eliminates the role of the doctor entirely, Posner and Weyl eliminate the patient, whose responses are "unpredictable" and "subjective."

But in the next paragraph, Posner and Weyl drop the established context of choice by doctors. They now speak of "individuals," like the ones who go "shopping for TVs, computers, or books," and Posner and Weyl conclude that such "individuals" do not need "richly detailed information" but need only "access to expert advice." The ready interpretation of all this is that "individuals" are patients and the "expert" is the doctor. But doctors, faced with a variety of distinctive patients and possessed of knowledge about each patient's circumstances, such as the way in which a patient initially responds to a given treatment, *can* make great use of information that is detailed beyond "a blunt permission or prohibition," as I discussed at length in reaction to Don Husereau's response to the K&B questionnaire. Furthermore, to the extent detail is not helpful, another possibility is that the FDA's judgment could be conveyed to the "expert" doctor as a mere certification. So one would think Posner and Weyl (2013) might see

objectively best treatment." They write: "While different individuals usually respond differently to different treatments, this reaction is usually as unpredictable to the individual as it is to the doctor treating her." But if "the" treatment had ever been administered to the individual before, the reaction could have been observed by the patient and by the doctor, thus increasing the predictability of that individual's reaction to any subsequent administrations of the drug.

prescription requirements plus certification as a sufficient remedy, but the words *prescribe, prescription, etc.*, do not appear in their article.

2. *Delayed and Uncertain Feedback.*—A classic mechanism that corrects poor decisionmaking in many settings and that actually allows individuals to learn far more about their settings than experts can is prompt and clear feedback about their success or failure. This has been demonstrated in a wide range of economic and psychological experiments. An important problem in medicine is that such feedback often comes with long delays and is often garbled by uncertain outcomes and placebo effects. Medicines that are inefficacious often do not show themselves to be so until the medication has been used for a long period, and efficacious medicines are often only effective on a small number of patients. Medicines can often have subtle but corrosive long-term side effects or may only have negative side effects with small probability. Therefore, whether on net the medicine is worth it is something that requires detailed scientific analysis, as is forced by the clinical trials required for FDA approval. Such settings are ideal for ex ante agency regulation rather than tort remedies because victims do not

learn of the harm until it is too late. (Posner and Weyl 2013, 1350-1351)⁷³

Only in the final sentence in this “Delayed and Uncertain Feedback” segment do Posner and Weyl offer an argument for intervention that goes beyond, say, knowledge production plus prescription requirements. The argument is that “ex ante agency regulation” is justified because “victims do not learn of the harm until it is too late.” It seems from the context that Posner and Weyl are concerned that the harm from taking some medicines may take so long to become manifest that the victims will not be able to, or simply will not, recover appropriate damages. Yet Posner and Weyl do not identify the means by which a regulator could identify, ex ante, those medicines which are inefficacious but only “show themselves to be so [after] the medication has been used for a long period” and “have subtle but corrosive long-term side effects.” The argument seems to lean on implausible assumptions about regulator foresight.

3. *Extent of Potential Danger.*—If you buy the wrong food, you may get sick, and if you buy the wrong cell phone, you may face a serious disruption to your work life. But the potency of medicines tends to mean that making the wrong decision has a very severe left tail that,

⁷³ I omitted two footnotes from this quotation, these being Posner and Weyl (2013, 1350 n.142, 1351 n.143). The first note provides two citations to psychology-journal articles about feedback and decisionmaking. The second cites a discussion of “the socially best level of litigation” by Steven Shavell (2004, 398ff.). None of this cited material discusses pharmaceuticals or approval regulation.

while it may be relatively low probability, can be devastating in the case it occurs. This makes extensive testing to ensure such outcomes are avoided crucial in medicine. (Posner and Weyl 2013, 1351)

I considered the possibility for overt disaster as perhaps constituting a market failure in pharmaceuticals above when discussing Peltzman (1974) and Reinhardt (2007). A further illustration is available here when considering both Posner and Weyl's concern about effects that will not manifest themselves for a long time and their concern about a "very severe left tail." Say there is a drug that will cause a disaster that will not become manifest for a long time. Since the regulator also does not know that the disaster is coming, would we rather have had the drug pass through pre-market approval and be trumpeted by the regulator as "safe and effective," or be in some alternate world where there has not been such a focal affirmation of the drug's worthiness? One might well imagine that consumption of such a drug would be greater under pre-market approval than under some other forms of intervention. I note that here Posner and Weyl do only affirm a need for "extensive testing" and not necessarily pre-market approval.

* * * * *

Posner and Weyl (2013) do not necessarily endorse address a regulatory regime for financial products that is fully analogous to pre-market approval. This creates, from the standpoint of one contemplating liberalization of pre-market approval, a temptation to

draw the analogy in reverse. Consider what Posner and Weyl say in a subsection of “Criticisms and Qualifications” that I quote here in its entirety:

3. Line-Drawing Problems and Issues of Generality.—Possibly the most difficult problem is defining a “financial product” for the purpose of review. Consider, for example, the CDS [Credit Default Swap]. Would the inventor of the first CDS have been required to obtain approval, or only the inventor of the first naked CDS, or the inventor of the first naked CDS to be used to insure against sovereign bonds, or just Greek bonds? Our tentative view is that the inventor of the initial CDS should be required to obtain agency approval. In the case of a financial product with many potential uses, the agency may determine that it will be approved only for certain uses (akin to the approval of new pharmaceuticals). The inventor or subsequent inventors may then seek approval for more specialized uses based on additional data or changes in market conditions.

A related problem could arise if investors choose to evade an FPA’s [Financial Products Agency] restrictions on a particular financial product by customizing a one-shot transaction that is functionally identical or closely related to the banned product. This is, however, a generic problem in financial regulation, and not a new one. The FPA and courts would need to do an ex post functional analysis to determine

whether the parties evaded the law through the manipulation of legal forms or had an independent and valid economic reason to enter into the transaction. Even if such adjudication is imperfect, preventing abusive products from being cheap and standardized would significantly raise the cost of using them and thus their prevalence.

One elegant solution to this problem would be to deprive the agency of the power to *block* financial products and instead give it the power only to *license* financial products. A financial innovator would be free to market a product without prior authorization, but state anti-wager and insurable interest laws would apply, and so subsequently a party could avoid enforcement of any contract where the financial product was used to gamble rather than to insure. To avoid the legal uncertainty, a financial innovator could apply to the FPA for a license or no-action letter that stated that the financial product satisfied our social welfare test and thus was lawful. A licensed financial product would be immune to challenge in court. Under this approach, people would (in theory) refuse to use financial products for gambling purposes because they could not enforce their payouts, while financial products mainly used for insurance purposes would be unaffected. (Posner and Weyl 2013, 1352-1353, emphases in original)

What Posner and Weyl call “line-drawing issues” have been vexing with regard to drugs. One of the ironies of pre-market approval is that it imposes bans on thoroughly tested products developed by sophisticated firms, while medical procedures and dietary supplements—drug substitutes that tend to be developed and produced in less intensely observed settings—are governed by far more permissive regulations. A similar irony is manifest in the liberal rules governing off-label use of approved drugs (Tabarrok 2000; Klein and Tabarrok 2008). We see that in the case of financial products, Posner and Weyl argue that an “elegant solution” for one of their concerns about line-drawing “would be to deprive the agency of the power to *block* financial products and instead give it the power only to *license* financial products” (2013, 1353). Very disappointingly, Posner and Weyl do not mention that there are any line-drawing issues in pharmaceuticals, even though in several other subsections of “Criticisms and Qualifications” (ibid., 1351-1357) they expressly draw the analogy.

Jerome Rothenberg (1993)

Rothenberg (1993) offers a rationale for pre-market approval in a review of Aaron Wildavsky’s *Searching for Safety* (1988):

When health and safety are at risk and the risk of irreversible and even fatal damages is high, it seems most appropriate that as much as possible be made of the current state of scientific knowledge. Screening requirements embody exactly this principle. Uncontrolled consumer use without such screening would not only represent high risk—given, say, the high safety-efficacy failure rate for new drugs—but would be a wasteful way to use currently inadequate knowledge. (Rothenberg 1993, 174)

Rejecting an efficacious new drug because it has serious side effects can represent a social loss if the side effects are outweighed by the good the drug may do. But Wildavsky assumes that regulation merely stops, deters, or discourages private actions rather than redirecting or channeling them. ... Wildavsky fails to allow that screening may steer competitive energies toward new avenues of improvement, rather than simply stopping innovation. The often-repeated tendency of pharmaceutical companies to continue searching for targeted products that meet safety standards, despite many early failures, illustrates how regulation does not necessarily curb innovation. The consequence of rejecting an effective new substance is more likely to be that a *better* one is soon developed than that no new substance at all is introduced.

Screening can be a process of learning, rather than of suppression.
(Rothenberg 1993, 174-175)

The FDA...approves many preparations that are only incompletely efficacious and have a variety of side effects. All preparations for cancer, AIDS, hepatitis, Parkinson's disease, muscular dystrophy—indeed, for all currently incurable diseases—that have been approved by the FDA are both incompletely efficacious and have a variety of side effects, some nearly as serious as the illness being treated. Physicians daily must struggle with the balance between partial benefits and serious side effects in deciding which drugs to prescribe. (Rothenberg 1993, 175)

[I]f one does not know how to recognize “beneficial” new drugs dependably without screening, and if the purpose of screening, with all its delays, is to point the way to devising new drugs that are *more* beneficial, then introducing “beneficial” new drugs without screening has a possibly serious indirect opportunity cost—namely, the delayed development and introduction of *even more* beneficial drugs—in addition to the direct cost of unnecessarily high side effects.

The net weight of both sets of direct and indirect costs is not easy to gauge empirically, so Wildavsky makes his case with examples

rather than solid quantitative evidence. How pervasive are well-publicized cases of apparently unwarranted delay? We certainly do not have quantitative estimates of the damage that has been directly prevented by screening, and indirectly by the incentives screening creates. More extensive, tightly analyzed data are required before we can make a trustworthy judgment about the issue. Wildavsky's anecdotal evidence is insufficient. (Rothenberg 1993, 175-176)

Rothenberg invokes the possibility of overt disaster as a market-failure justification for pre-market approval. He also argues that pre-market approval can push producers to develop better drugs than they otherwise would, but this argument is effectively an objection to a claim of 'government failure' and not a claim of market failure. In other words, Rothenberg does not establish that there is a market failure that should be redeemed, but rather he suggests that pre-market approval is itself an engine of innovation. He writes: "The consequence of rejecting an effective new substance is more likely to be that a *better* one is soon developed than that no new substance at all is introduced." This is an argument for not rejecting only the first "effective new substance" but also the second, third, and every subsequent effective substance. In lieu of bans on effective substances, why not merely support studies of the efficacy of commonly used drugs—followed by information campaigns and appropriate adjustments to government drug purchasing?

Carolyn Hughes Tuohy and Sherry Glied (2011)

In their handbook chapter “The Political Economy of Health Care,” Tuohy and Glied discuss intervention and pre-market approval in this section:

4.1.2 Information Gaps

A second longstanding function of government in health care is to redress informational gaps through regulatory action. The complexity of biological processes means that consumers face very high information costs in assessing the health implications of various goods and services, and may be vulnerable to undue influence from providers. Initially, government regulation of health care focused on protecting the safety of consumers. Many of the earliest incursions of government into the regulation of product quality were in the sphere of health (for example, the regulation of food and drugs dates back to the 1920s). This protection also extended to licensure and regulation of the health care professions. The information gap between providers and consumers of health care services means that consumers must enter into an “agency relationship” with providers, trusting them to act in the consumer’s best interest.... The typical mode of regulating this agency relationship has

been for the state to recognize the authority of professional self-regulatory bodies and progressively integrate them into the governance apparatus of the state (Starr 1982). In effect, this establishes a “second-level” agency relationship between the state and the professional body.

From an economic perspective, much of this regulatory function has an explicit or implicit redistributive component. In many arenas, private organizations offer complementary systems of quality validation (the “Good Housekeeping” seal of approval; specialty society certifications; and hospital quality approval organizations such as the Joint Commission on the Accreditation of Healthcare Organizations). The requirement that purveyors of health care associated goods and services meet minimal government standards in order to practice seeks to protect those who would be unaware of, or unwilling to pay a premium price for, privately accredited goods and services.

The regulatory functions of government extend beyond ex ante development and enforcement of quality standards. Governments also develop and maintain the legal infrastructure that enforces ex post quality standards through liability regimes. The rules governing the liability of health care goods and services providers (products liability and malpractice litigation, in particular), have been a focus of economic study, especially in contexts where these systems are very costly. (Tuohy and Glied 2011, 59-60)

The only possible justification Tuohy and Glied suggest is that “minimal government standards...protect those who would be unaware of, or unwilling to pay a premium price for, privately accredited goods and services.” Why not merely require labeling with the FDA’s judgment?

F. M. Scherer (2000)

In his handbook chapter “The Pharmaceutical Industry,” Scherer (2000) did not directly present a market-failure justification for pre-market approval but instead described the status quo regulations and then posed a series of “fundamental philosophical questions” and “perplexities”:

Granting or denying permission for full-scale marketing of a new drug is an exercise in decision-making under uncertainty. Clinical test insights can be sharpened through the use of appropriate statistical methodologies, but they cannot eliminate uncertainty, especially for adverse side effects of very low incidence. Decision-makers must weigh the risk of Type I errors—approving a drug when it is not truly safe or effective—against the risk of Type II errors—withholding from the

market entities that are truly effective and safe. ... In governmental agencies, there is a natural tendency toward placing more weight on avoiding Type I errors, since officials who approved a product that leads to cancer or malformed babies will be singled out for castigation in public fora. The tradeoff can be narrowed by increasing the size of clinical trial samples, but that solution increases costs, possibly discouraging the development of some drugs, and it is likely also to delay the availability of new drugs.

Several further questions follow. If uncertainty is high but the possibility of life-saving benefits is also substantial, shouldn't a regulatory agency illuminate the problematic tradeoff and let individual physicians and/or patients make their own risk-taking decisions, rather than being restrained by the choice of a bureaucracy? Stung by criticism that its decision-making was denying potentially vital therapies to patients with life-threatening diseases, the U.S. FDA began during the 1980s to make increasing use of "compassionate NDA" procedures under which experimental drugs that have not yet been approved formally are made available to physicians. For HIV drugs, it also waived the requirement that double-blind tests be conducted, for to assign a patient randomly to the placebo group could be tantamount to imposing a death sentence.

Recognizing such exceptions, one must ask the further question, why should a regulatory agency be the ultimate decision-maker on whether *any* new drug can be used? To be sure, absent regulatory requirements, drug manufacturers might perform too little clinical testing to ascertain whether a drug is superior to existing alternatives. Meager testing was the norm in the pre-thalidomide era. An information market failure may need correction. But why doesn't the regulator merely require appropriate testing and disclosure of test data, letting physicians decide from the data whether the drug is safe and efficacious? If there is an argument for regulation of *whether* new drugs may be marketed, it must lie in a further information failure—e.g., from the possibility that most physicians are too busy to make well-informed independent decisions.

Carrying the debate one step farther, why should *prescriptions* be required to obtain drugs? They are not required for over-the-counter drugs or, in many less-developed nations, for any available drug. The prescription system implies that patients are unable to make well-informed decisions about their own welfare, so physicians must act *in loco parentis*. That may be true, but obtaining a prescription imposes costs, and Sam Peltzman's (1987) statistical analysis suggests that there is no clear indication of higher poisoning or mortality rates in middle-

income nations where prescriptions are not required. (Scherer 2000, 1314-1316)

As in his response to the K&B questionnaire, which I addressed above, Scherer's bottom-line justification of pre-market approval here is that "most physicians are too busy to make well-informed independent decisions."

Charles Phelps (2012)

In his textbook *Health Economics*, Phelps writes:

In reviewing the scope of regulations that the U.S. health care system has experienced over the past half-century, one can say readily that the myriad regulatory interventions come from one of two related purposes: to control the introduction of new products into the market (such as drugs and medical devices) or to manage somehow what the political system considers as important failures in the market functioning. The "market failures" might fall in the realm of price controls to deal with escalating medical care costs (a consequence, some might say, of growing insurance coverage or even because of the not-for-profit nature

of major health care providers). In response to such concerns, our society has experienced many forms of price controls and limitations on entry (“certificate of need laws”).

Other areas in which market failure looms as a concern involve the quality of care and concerns that consumers of health care cannot judge quality effectively. Following such concerns, persistent regulation of quality has occurred through licensing of providers (doctors, dentists, nurses, therapists, pharmacists, etc.) and requiring large-scale testing of new drugs and medical devices before they can be marketed in this country. (Phelps 2012, 427-428)

A number of regulations [in the health care sector]...directly attempt to improve quality of treatment. FDA rules to control safety and efficacy of drugs and medical devices provide an obvious example, as does licensure of various medical personnel (doctors, dentists, nurses, etc.). In both cases, private provision of information (advertising of drug quality, certification of provider quality by “boards”) provides a nonmandatory alternative that coexists with mandatory licensure. In most (if not all) cases, private certification provides evidence of a higher standard of quality than the mandatory licensure requires.

Many regulatory activities, whether aimed at controlling cost or enhancing quality, have the obvious side effect of changing the nature of

competition, primarily because of the implicit or explicit effects on entry by competitors. ... FDA rules (until the 1984 revisions) considerably restricted competition, especially in the entry of “generic” products. ...

Careful economic analysis of regulation in the health care sector remains an important realm of study; every regulation considered in this chapter has the *potential* for providing some social benefit, and none is unambiguously without merit. Each, in turn, has the *potential* for creating economic mischief, either through effects on competition or quality, or combinations thereof. Thus, we leave the discussion of regulation in the health care sector with the usual economist’s two-handed evaluation: “On the one hand, they might be good, and on the other hand . . .” (Phelps 2012, 466)

Phelps offers only “concerns that consumers of health care cannot judge quality effectively” as a market-failure justification of pre-market approval. From his lack of elaboration and the tone of his discussion, I am tempted to infer that Phelps does not think there is much to said concerns.

Robin Hanson (2003; 2008)

Hanson (2003) offers a paper titled “Warning Labels as Cheap-Talk: Why Regulators Ban Drugs.” Hanson does not examine what market imperfections may exist with regard to drugs, but rather he presumes such imperfections exist and that a powerful regulator aims to remedy such imperfections indirectly, by modifying the quantity consumed. Hanson suggests that a regulator bent singlemindedly on fulfilling such a charge might be expected by consumers to deceive them (2003, p. 2014). Hanson claims that such suspicion of deception will create a situation in which the regulator can sometimes come closer to achieving its quantity targets by banning drugs rather than merely communicating information about the drugs. Hanson has also published a discursive essay on possible justifications for medical paternalism (Hanson 2008). In that essay he explores possible motivations that an “advisor” may have, i.e., he introduces the notion that the advisor is not merely singlemindedly bent on correcting determinate consumer error, and thus he contextualizes the formal model of Hanson (2003) as a special case.

Do Hanson’s efforts supply a link between market failure in pharmaceuticals and the particular remedy of pre-market approval?⁷⁴ Hanson’s primary exploration relates to a supposed informational market failure: There is “consumer ignorance about product

⁷⁴ Hanson himself does not seem to think so. He concludes his 2008 essay by asking advocates of “limits on the food and drugs people can buy” to “make some effort to explain...exactly why you think your paternalism is justified” (p. 913).

quality. Regulators are presumed to know which health aids are good and which are bad” (2003, p. 2014). His model incorporates an assumption that the FDA has private information and has two-way interactions with consumers that can be modeled as a “cheap-talk signaling game” (ibid.). But under pre-market approval, drug producers (and others as well) are aware of the results of clinical trials and could disclose them—and in the instance that FDA leaders were to give into “any small temptation to...lie,” such disclosure would seem rather likely. Public availability of information that the regulator uses in making its judgments would call into doubt the justificatory power of the signaling model Hanson uses (viz., Crawford and Sobel 1982). The model can still apply if the regulator *believes* that it has private information it cannot credibly convey to the public, and as a result of that belief it may often impose bans, but such would be an explanation of bans and not a justification of them.

Hanson lists several other possible market imperfections that may motivate regulators to ban drugs:

Regulatory product bans and limits on quality have been explained as due to regulatory capture, or as a public interested response to inefficient monopolist quality menus (Mussa and Rosen, 1978), inefficient signaling (Shapiro, 1986), consumer irrationality (Spence, 1977), and negative use externalities. Negative externalities are mentioned especially regarding recreational drugs, such as alcohol.

Smoking externalities are said to exist between people and within people. (Hanson 2003, pp. 2013-2014, some citations omitted)

Regulatory capture would of course only be an explanation and not a justification of bans. There are a raft of laws that deal specifically with “negative externalities” that may be associated with “recreational drugs” and smoking. While the severity of certain punishments under those laws is harsher when drugs unapproved by the FDA are involved, I am unaware of any published argument that such externalities justify pre-market approval of drugs in general, and neither does Hanson suggest so here.

Michael Mussa and Sherwin Rosen analyze “monopoly pricing problems involving what a businessman might call a product line, a quality-differentiated spectrum of goods of the same generic type” (1978, 301). They provide an example in which such a monopolist can alter quality levels in order to induce “less enthusiastic consumers to buy lower quality items, opening the possibility of charging higher prices to more adamant buyers of high quality units” (ibid., 306). In the context of pharmaceuticals, rather than evoking market power as being caused by patent protection as did Philipson and Sun (2008), Mussa and Rosen (1978) would evoke a firm having market power over a *class* of drugs, and then declining to bring a middling drug to market in favor of a weaker drug, in order to raise prices on a superior drug. It seems impossible to believe this scenario could come up frequently enough to justify pre-market approval, as opposed to justifying only specific instances of ordinary antitrust enforcement.

Carl Shapiro (1986) builds a model to examine occupational licensing. He finds that:

Licensing may improve welfare by altering sellers' incentives, i.e. by reducing the marginal cost of quality. It cannot operate effectively absent the formation of professional reputations, however, and is unlikely to raise welfare if the marginal cost of quality is large relative to the value consumers place on it.

Even when it raises aggregate consumer surplus, licensing cannot constitute a Pareto Improvement. Those consumers who value quality relatively little are made worse off by licensing. In general, licensing will raise the average quality of service in the market, but the cost of doing so may be so great as to decrease aggregate consumer surplus.

Shapiro (1986) offers only an indeterminate result in terms of the aggregate economic efficiency of professional licensing, along with questionable distributional effects, and of course no empirical content related to pharmaceuticals.⁷⁵

⁷⁵ Shapiro (1983) is a similar study of "high quality products"; see *supra* note 27.
278

Michael Spence (1977) builds a formal model of “Consumer Misperceptions, Product Failure and Producer Liability.” Spence mentions three interventions that could address the possibility of product failure and the need for insurance against it, the first two being “direct regulation of safety” and “a programme to inform consumers.” But Spence describes the paper as being an investigation of the third intervention he lists, “imposing liability on the producer above the levels that are voluntarily undertaken, to supplement the incentives that are not provided by demand” (1977, 561). Nowhere in the article does Spence explain what he means by “direct regulation.” In his model, an industry liable for product failures selects a level of “reliability,” which is the probability that a product “does not fail.” The alternative interventions, direct regulation and informing consumers, are not modeled. Of “direct regulation,” Spence merely writes: “Direct regulation of reliability or safety and insurance requires full knowledge of consumer preferences and costs or technology. It does not require knowledge of consumer perceptions. ... Direct regulation may be preferable when the loss to the consumer exceeds the seller’s ability to pay. ... [D]irect regulation should be substituted for liability in areas where losses are catastrophic” (Spence 1977, 566-567).

Thomas Getzen (2010)

In his textbook *Health Economics and Financing*, Getzen has a chapter titled “Public Goods and Public Health” within which is a section “Information” and a subsection “Rational Consumer Ignorance.” The subsection reads as follows:

Why does the government have a better information base for making decisions than most citizens? Because the government paid for it. From safety standards for seatbelts to the efficacy of vitamin supplements, millions of dollars have been spent to determine the best possible answers. Massively wasteful duplication would result if each consumer collected such information individually. If consumers banded together to share the costs of gathering information, such banding would constitute a form of government. Consumers are rationally ignorant of many health and safety issues because it is more efficient to have the government collect information once than for each of us to do it separately. Rational consumer ignorance is sensible free riding. Even for a private good, such as a bottle of vitamins, it is cheaper to perform quality control once in a government laboratory than to do it over and over again in each individual’s home.

Consumers remain rationally ignorant by delegating their decision-making powers to the government because it is more efficient

for them to do so—they are being smart by staying stupid! Thus, the Food and Drug Administration (FDA) tests the safety of food and drugs, the Environmental Protection Agency (EPA) conducts studies on the effects of pollution, and the Department of Transportation (DOT) monitors the safety of highways and motor vehicles. (Getzen 2010, 358)

In another, earlier chapter of the book, “Pharmaceuticals,” Getzen provides an account of the “History and Regulation of Pharmaceuticals.” The first and last paragraphs of that account are as follows:

The regulation of the pharmaceutical industry and its products evolved during the twentieth century in response to increased potency, effectiveness, and toxicity of drugs. Until the late 1800s, most “pharmaceutical preparations” had an immediate effect of making the patient feel better, although in most instances they did little to cure the underlying disease. This meant that patients could directly evaluate the benefits of the drug and did not need extensive guidance from health care professionals in choosing which products to use. (Getzen 2010, 256)

Regulation of the pharmaceutical industry has evolved over the past hundred years by responding to the perceived needs for consumer

protection and industry development, attempting to balance the benefits and costs of regulation. What began as a requirement for adequate labeling, ensuring that the public was protected from adulterated or misrepresented products, grew into a system in which consumers no longer make choices about the drugs they receive but rely on their physicians (and sometimes even third-party payers) to make these choices for them. (Getzen 2010, 259)

Getzen writes as if there is no valuable information local to the patient, and so consumers may as well remain “stupid,” “delegating their decision-making powers to the government,” which has “the best possible answers.” He also states that any voluntary consumer association that gathered information on drugs “would constitute a form of government.” He does not explain why government cannot just communicate its judgment to physicians and patients, perhaps via labeling, nor why the government should implement bans on the basis of quality. His discussion seems to offer little beyond elementary versions of the formulations *the regulator is evidently excellent* and *the individual and the nation are the only meaningful units of analysis*.

Sherman Folland, Allen Goodman, and Miron Stano (2007)

In their widely used textbook *The Economics of Health and Health Care*, Folland, Goodman, and Stano do not link pre-market approval with any particular market failure. In a chapter on “The Pharmaceutical Industry” they provide a short history of pharmaceutical regulation in the United States, and then say:

The economic approach is to weigh the gains in safety and efficacy against the cost of delaying patients from utilizing useful products. Economists also are concerned about the potential stifling of innovation caused by regulation and its adverse effects on competition. (Folland, Goodman, and Stano 2007, 363)

A later chapter, “Government Intervention in Health Care Markets,” begins with a general economic lesson on types of market failure, followed by a section on forms of intervention, then to instances of intervention that impact health care. But they do not tie a specific market failure or failures to the interventions. Under “Food and Drug Administration,” they merely reiterate:

The economic issues of drug regulation pit the relative gains in drug safety and efficacy against the discouragement to innovation and the

delays in availability attributable to the approval process. (Folland, Goodman, and Stano 2007, 417)

SYNTHESIS OF LITERATURE ON
MARKET FAILURES RELATED TO PRE-MARKET APPROVAL

Much of what is found in the literature on market failures related to pre-market approval does, I think, boils down to one or other of the formulations synthesized above from the responses to the K&B questionnaire. For example, the concern that *doctors misplace their trust* is evident in Peltzman's (1974) summary of arguments for the 1962 Amendments. The idea that *knowledge that is too expensive to communicate to doctors* is also manifest in Peltzman (1974), and I see it too in Malani and Philipson (2012) and Tuohy and Glied (2011). The position that *the regulator is evidently excellent* is found in Danzon (2011) and Getzen (2010). Some combination of these formulations is also effectively latent when Carpenter (2009c) and Posner and Weyl (2013) advocate pre-market approval without examining prescription requirements as an alternative remedy for knowledge-related concerns.

Below I suggest there are two major formulations in the literature that are importantly distinct from those listed in the synthesis of questionnaire responses. These formulations are variants upon items aired at least tangentially by one or more supporters of pre-market approval who responded to the K&B questionnaire, but they appear multiple times and are raised more strongly in the literature.

Key formulation or argument: *There is potential for disaster*

A few respondents to the K&B questionnaire offhandedly mentioned thalidomide (Berger, Culyer) or briefly raised the specter of death or tragedy (Brazier, Scherer). The possibility of disaster is central in the discussions by Peltzman (1974), Reinhardt (2007), and Posner and Weyl (2013) of what it is that pre-market approval is intended to remedy. Could such a risk itself be said to comprise a market failure in pharmaceuticals? The historical record does show instances of great popular enthusiasm for novel treatments that were later widely judged ineffective. Perhaps there is something in the nature of novelty and hope for the treatment of disease that frequently and inappropriately overrides natural concerns about unusual new substances, thus creating a disquieting harmony between patient and physician tastes for risk and manufacturers' optimism about newly patented pills. Whether and how a regulator could avoid being swept up in such a tide, and what means any rock-like regulator should use to break the waves, are questions that would need to be addressed. As I wrote in reaction to Peltzman (1974), the particular intervention of pre-market approval could create risk of disaster: it is at least plausible that a regulator's approval of a hazardous drug could create a larger disaster than might occur if a similar hazardous drug were to enter the market in an environment where consumer skepticism is higher. I do not think this line of argument puts product bans entirely off the table in situations where disaster is possible. Hanson (2003) does usefully point out that when a regulator has the power to ban products, then the lack of a

ban can convey information. It seems possible that a regulator could be understood as empowered to ban in certain extraordinary situations while not also asserting a general mission of “ensuring drugs are safe and effective” as is done under pre-market approval.⁷⁶ But I find it unlikely that banning alone can satisfactorily resolve difficult situations; as I discuss above, production and dissemination of knowledge were key in the case of Laetrile. Also, an extraordinary ‘situation’ does imply a limited time horizon, so such a situation could justify only a temporary product ban, as in the case of thalidomide. As for permanent interventions that stop short of pre-market approval but address the possibility of disaster, one might consider a requirement that doctor prescriptions of new drugs go through additional levels of scrutiny, as I suggested in reaction to Peltzman’s narration concerning “entranced” patients.

Key formulation or argument: *Producers bear insufficient liability*

In responses to the K&B questionnaire, Kenneth Arrow proposed that drugmakers “do not have the right incentives to assure efficacy and safety,” and F. M. Scherer offered the thought that “despite the threat of significant tort liability for harmful drugs and devices, manufacturers have been less than diligent in ensuring that pre-market testing is adequate and that public health hazards are avoided.” Reinhardt (2007), Philipson and

⁷⁶ See <http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm>.

Sun (2008), and Posner and Weyl (2013) all argue that limits to the legal liability faced by firms are a rationale for regulatory action. Philipson and Sun (2008) developed the idea most thoroughly and credibly, but they did little if anything to connect their concerns about liability to specific remedial interventions. I think the interplay between liability and pharmaceutical regulation is likely a fertile ground for more inquiry.

CONCLUSION

What justifies pre-market approval? Such a question is bound up with our presumptions about political economy, particularly the presumptions for liberty and for the status quo, and our views on what argumentation or evidence is sufficient to overcome or buttress those presumptions. The economists' literature tends to lay emphasis on the presumption for liberty, which treats Adam Smith's system of natural liberty as a presumed known 'baseline' or vantage point. Economists can then proceed to discuss potential 'market failures', the magnitudes of associated costs, and whether remedial interventions might be justified. Much other ('noneconomic') discourse may be viewed as proceeding from a presumption for the status quo. Proposals to alter the status quo can be discussed, and efforts may be made to consider the magnitude of the costs and benefits of a given proposal. But the universe from which one would draw such proposals can seem unlimited, or even formless—when attempting to put forward a model, the analyst may find it exceedingly difficult to characterize or 'locate' the status quo. By contrast, Smith's system has provided the economists with a place to stand, on which the analytical structure of market-failure argumentation has been built.

None of the economists surveyed by K&B who support the pre-market approval policy referred to a focal citation on the topic; rather, they almost all seemed to shoot

from the hip, and those who did refer to published research did not cite anything concerned with pre-market approval *per se*. While there is the possibility that a good argument for pre-market approval can be put together off the cuff, I don't see that that was achieved by any of the respondents. Almost all the economists surveyed could point to a market failure or failures that may plausibly exist and perhaps even powerfully affect the market for pharmaceuticals, but none made an explicit and well reasoned connection between those market failures and the specific remedy of pre-market approval. Many said patients or doctors are biased; many said the FDA has an advantage in obtaining or analyzing information about drugs; few if any can be said to have critically compared pre-market approval against other methods of countering bias or generating actionable knowledge. Noncoercive or less coercive policy alternatives, such as informational campaigns, universal prescription requirements on new drugs, and refusal by government to purchase drugs it deems unworthy, went unconsidered or were rejected.

The review of literature on pre-market approval, perhaps surprisingly, suggests to me the tentative conclusion that the closest thing economists have to a market-failure rationale may be based in the prospect that overt disasters like Elixir Sulfanilamide and thalidomide can occur. Uwe Reinhardt (2007) in particular emphasizes that such disasters are politically difficult to tolerate, and he notes that firms' pecuniary incentives, due to the limitations of liability, may by themselves be insufficient to deter inappropriate risk-taking. Reinhardt suggests that one should take as given that overt disasters all but must be averted—that economists cannot rely on a “collectivist calculus,” which says net lives

(or life-years, QALYs, etc.) saved is the appropriate metric, to carry the day. In contemplating Reinhardt I am reminded of John Maynard Keynes's complaint about economists who set themselves too easy a task by waiting for a "long run" to arrive (1923, 80); I would like to interpret Reinhardt as not counseling acceptance of 'statistical' disaster but rather as admonishing us to look hard for a win-win solution. Reinhardt's argument can use more elaboration, but at a minimum it should suffice to justify interventions that provide a very high level of assurance that large *mistakes*, such as that which caused the Elixir Sulfanilamide disaster, are avoided.

But I did not find in the literature strong justification for other elements of pre-market approval; instead, there were some affirmations that the case for those elements is weak. I found agreement among multiple sources that Peltzman (1973) remains to this day the only attempt to do a cost-benefit analysis of pre-market approval (see *supra* note 4). Major health economics textbooks by Phelps (2012) and Folland, Goodman, and Stano (2007) essentially leave empty the spaces where they are supposed to identify the market failures that justify pharmaceutical regulation. Handbook chapters by Scherer (2000) and Tuohy and Glied (2011) offered token justifications. Much of Daniel Carpenter's "Harvard Project" is readily interpreted as a reaction to perceived failure on the part of economists to justify pre-market approval. Eric Posner and Glen Weyl (2013) combine the highest level of aggressive support for approval regulation with low levels of knowledge and curiosity about pharmaceutical matters.

In lieu of a clear-cut justification for pre-market approval overall, I take from the K&B questionnaire responses and literature review the strong sense that additional study can yield guidance as to what parts of pre-market approval should be retained, which jettisoned, and which altered. Below I list four areas where I am particularly optimistic for the prospects of such study.

Study the informational effects, including those on consumer confidence, of product bans

Kenneth Arrow and others suggest that pre-market approval induces production of more information about drugs. Daniel Carpenter has argued that pre-market approval leads to greater consumer confidence in drugs. But in my view there is not nearly enough theory or evidence to affirm pre-market approval as a good means, let alone the best means, of delivering such effects—and in the case of the consumer confidence effects, not even enough to show that such effects are desirable. To advance such arguments, research could be done—or synthesized—to disentangle the effects (informational and otherwise) of a ban on drugs deemed low-quality from the effects of required testing (and other testing), the effects of certification by a government regulator (and other certifications), and so forth. Research on how doctors come to place their trust in drugs is also relevant, not least as it can address the matter of whether there is any systematic tendency toward ‘overconfidence’ or ‘underconfidence’, what ‘market statistics’ doctors

may use in their decisionmaking, and whether such use tends to drive good products out of the market as predicted by “lemons” theory.

Study the safety-efficacy distinction to see if it can form a plausible basis for liberalization

Of the possible partial liberalizations of pre-market approval that come to mind, a reform that instructs the FDA to relax its efficacy standard seems very appealing. But it is not at all a simple matter to separate safety concerns from efficacy concerns, as I discussed in reaction to Marc Berger’s survey responses. One may somewhat plausibly claim that the key historical events leading to the adoption of pre-market approval were disasters caused by insufficient safety, not insufficient efficacy. But beliefs about the benefits from taking a drug will play a major role in the types of patients who take a drug, the number who take it, and attitudes toward what level of uncertainty about a drug’s risks is acceptable. When thinking about certification or pre-market approval, we can imagine that assurance of efficacy combined with hidden safety hazards would tend to amplify disasters, while disabusing mistaken beliefs in a drug’s efficacy should mitigate or prevent disasters. My tentative suggestion is to explore the possibility that a regulator may be able to project an identity of working to challenge efficacy claims that are made, without claiming that it assures the efficacy of all available drugs. This would comport

with the argument by David Healy that the method of testing drugs in clinical trials “is of greatest use when it demonstrates drugs either do not work or have minimal effects” but “has in company hands become the main fuel of the latest bandwagons” (2012, 90).

Study the nature of demand for drugs about which little is known

Do patients or doctors have a tendency to inappropriately consume or prescribe new drugs too soon, when there is an insufficient base of knowledge to justify such use? If so—and the historical record is I think suggestive that there may be such a tendency—then interventions that produce knowledge about or restrict drugs during the period when they are ‘new’ and it is ‘too soon’ may be desirable. Those aspects of pre-market approval that mitigate the possibly adverse effects of ‘newness’ are thus, I venture to say, perhaps not the first aspects that should be considered for liberalization. Reducing pointless delays is of course desirable. But imagine that one were made to choose between two paths for careful research into reform: (1) study of liberalizing a standard for efficacy, which one expects would allow *more* new drugs to reach the market, and (2) study of liberalizing requirements for production of knowledge, which one expects would allow new drugs onto the market *sooner*. My tentative sense is that a researcher should opt for the first path.

Study the 'line-drawing' problem

Those examining pre-market approval should take care to integrate their views into a broader outlook on regulation and markets. Particularly to be resisted is any temptation to treat new pharmaceuticals, or medicine in general, as a well defined space that can be analyzed in isolation; one may draw a line, but the enormous continent of 'alternative medicine' is all around. Any good case for this or that aspect of pre-market approval should discuss why applying a similar intervention to drug substitutes is or is not a good idea, and why off-label use of approved drugs should or should not be permitted.

Final remarks

In a recent article comparing Milton Friedman unfavorably to Friedrich Hayek, the Nobel laureate Robert Solow wrote:

Friedman could be...rather lax in finding support for his own opinions. To take one example, Friedman proposed abolishing the Food and Drug Administration

because the harm done by its excessively cautious delays in approving new drugs outweighed the dangers that would come from simply making drugs freely available on the open market. How could he, or anyone, possibly know that? One can indeed imagine an immensely complicated empirical study, requiring all sorts of assumptions and approximations, the outcome of which would inevitably be clouded by complexity, guesswork, and great uncertainty. But that would win no hearts or minds. Friedman's confident assertion just sounds like fact-based knowledge. A different sort of person would have looked for ways to speed up the FDA's approval process. (Solow 2012)

Solow is broadly correct about the difficulty of performing a convincing empirical study to show that pre-market approval, on the whole, is a net loss for the world. But then he seems to say that Friedman never should have bothered advocating for the FDA's elimination: "A different sort of person"—seemingly, the sort who would have more of Solow's esteem than did Friedman—"would have looked for ways to speed up the FDA's approval process." I interpret Solow as saying that the minimal action is better *because* the radical action is harder to support with a convincing empirical study. But realize, Solow's logic equally implies that the FDA's continued existence, relative to its abolition, would be hard to defend with convincing empirics. With regard to the FDA, Solow grants a large presumption to the status quo. But what if we were currently living under a pervasive system of wage and price controls? What would we say it is that justifies the radical move to dump *that* whole system?

I would suggest that small changes in policy are also difficult to defend, convincingly, with empirics—perhaps not much less difficult than big changes would be. Say we set out to predict the effects that just a one percent reduction in ‘FDA cautiousness’ would have. Where exactly would the FDA cut those corners? Say we were able to propose some fairly definite piece of caution to eliminate. How much would this change reduce approval times? We can’t approximate that without careful research. Only after that point could we begin to approach the question of the change in societal welfare that would result. And any trained economist, contemplating the process to obtain an answer, would envision exactly what Solow says is necessary to judge for or against the entire FDA, viz., “an immensely complicated empirical study, requiring all sorts of assumptions and approximations, the outcome of which would inevitably be clouded by complexity, guesswork, and great uncertainty.” And after conducting such a study, one might expect to find that the effects of a tiny policy shift are tiny, as the effects of a large policy shift may be large, and so it may well be comparably difficult to convince an audience that one’s assumptions are sufficiently precisely appropriate to justify one’s corresponding determinations regarding the signs of the predicted changes in the desiderata. Such studies have a role to play, but not absent appropriate attention to the power of undergirding presumptions, beliefs, and ideas.

Ideology clouds our vision on important matters. For one who wishes to buttress the institution of pre-market approval, it is surely tempting to dismiss as inappropriately

motivated the authors of scholarship that is critical of the institution. For one inclined to challenge the institution of pre-market approval, it is tempting to dismiss the majority opinion among at-large economists as being ill founded. We call on ourselves to do better than this, but it is not easy. Presuming for the moment, though, that the challengers are broadly correct, the politically aware person might reasonably ask of them whether there is any real prospect of major institutional reform. Perhaps there is not. Even so, I see value in economists' work to develop and maintain the skeptical narrative on pre-market approval. Young economists who come to believe that the FDA was formed from political expediency, that many of its effects are unfortunate, and that it is not easily reformed, will be wary of the next plea that any comparably unjustified intervention be newly imposed upon some other vital area of industry.

APPENDIX A

In propounding the presumption for liberty, Adam Smith emphasized local knowledge and incentives. Here is a selection of relevant quotations.

“Every man, as the Stoics used to say, is first and principally recommended to his own care; and every man is certainly, in every respect, fitter and abler to take care of himself than of any other person. Every man feels his own pleasures and his own pains more sensibly than those of other people. The former are the original sensations; the latter the reflected or sympathetic images of those sensations. The former may be said to be the substance; the latter the shadow” (1790, 219).

“These [casuistic rules to direct our conduct] it is often impossible to accommodate to all the different shades and gradations of circumstance, character, and situation, to differences and distinctions which, though not imperceptible, are, by their nicety and delicacy, often altogether undefinable” (1790, 227).

“That wisdom which contrived the system of human affections, as well as that of every other part of nature, seems to have judged that the interest of the great society of mankind would be best promoted by directing the principal attention of each individual to that

particular portion of it, which was most within the sphere both of his abilities and of his understanding” (1790, 229).

“The administration of the great system of the universe, however, the care of the universal happiness of all rational and sensible beings, is the business of God and not of man. To man is allotted a much humbler department, but one much more suitable to the weakness of his powers, and to the narrowness of his comprehension; the care of his own happiness, of that of his family, his friends, his country...” (1790, 237).

“It is impossible by language to express, if I may say so, the invisible features of all the different modifications of passion as they show themselves within” (1790, 328).

“What is the species of domestick industry which his capital can employ, and of which the produce is likely to be of the greatest value, every individual, it is evident, can, in his local situation, judge much better than any statesman or lawgiver can do for him” (1776, 456).

“Jack of all trades will never be rich, says the proverb. But the law ought always to trust people with the care of their own interest, as in their local situations they must generally be able to judge better of it than the legislator can do” (1776, 530-531).

“The interest of the corn merchant makes him study to do this as exactly as he can; and as no other person can have either the same interest, or the same knowledge, or the same abilities to do it so exactly as he, this most important question of commerce ought to be trusted entirely to him; or, in other words, the corn trade, so far at least as concerns the supply of the home-market, ought to be left perfectly free” (1776, 534).

“The sovereign is completely discharged from a duty, in the attempting to perform which he must always be exposed to innumerable delusions, and for the proper performance of which no human wisdom or knowledge could ever be sufficient; the duty of superintending the industry of private people, and of directing it towards the employments most suitable to the interest of the society” (1776, 687).

APPENDIX B

To see if any important market-failure arguments for pre-market approval are missing from the synthesis of K&B survey responses above, I systematically reviewed relevant reading materials assigned in health economics courses at several top universities.

I began the review by selecting both the top three U.S. economics departments and the number-one UK economics department “in the field of health economics” according to the IDEAS service of the Federal Reserve Bank of St. Louis, which as of June 2014 were Princeton, Harvard, MIT, and York.⁷⁷ To these four, for some broadening beyond these departments, I arbitrarily added George Mason University (where I am enrolled) and the University of Texas (to which I have familial connections). I then attempted to find any syllabi from health economics courses offered by these schools, and to identify works listed on the syllabi that seemed to me likely to contain material related to FDA pre-market approval, and then to review those works and compile any material in them that is related to pre-market approval.

The universities are listed below. I describe the methods I used to find the health economics courses, and then I list the courses. Under each course I list those works found

⁷⁷ <https://ideas.repec.org/top/top.he.html>

on the course syllabus that I guessed might contain material related to pre-market approval. Those works that upon review I found to contain argumentation related to pre-market approval that was necessary to address in this dissertation are starred.

Princeton

At <http://registrar.princeton.edu/course-offerings/>, I searched the Spring 2013-2014 ECO courses for “health,” finding two courses. I also searched Fall 2013-2014 ECO courses for “health,” finding none.

ECO 332 Economics of Health and Health Care (instructor: Uwe Reinhardt)

Berndt, Ernst, and Joseph Newhouse. 2011. A Primer on the Economics of Prescription Pharmaceutical Pricing in Health Insurance Markets. NBER Working Paper 16879. National Bureau of Economic Research.

*Folland, Sherman, Allen C. Goodman, and Miron Stano. 2012. *The Economics of Health and Health Care*, 7th ed. Prentice-Hall.

Reinhardt, Uwe E. 2001. Can Efficiency in Health Care be Left to the Market? *Journal of Health Politics, Policy and Law* 26(5): 967-992.

*Reinhardt, Uwe E. 2007. The Pharmaceutical Sector in Health Care. In *Pharmaceutical Innovation: Incentives, Competition, and Cost-Benefit Analysis in International Perspective*, eds. Frank A. Sloan and Chee-Ruey Hsieh, 25-53. Cambridge University Press.

Sloan, Frank A., and Chee-Ruey Hsieh. 2008. The Effects of Incentives on Pharmaceutical Innovation. In *Incentives and Choice in Health Care*, eds. Frank A. Sloan and Hirschel Kasper, 228-262. MIT Press.

ECO 565 Health Economics I (Janet Currie)

Goldman, Dana, and James P. Smith. 2005. Socioeconomic Differences in the Adoption of New Medical Technologies. *American Economic Review* 95(2): 234-237.

McGuire, Thomas G. 2000. Physician Agency. In *Handbook of Health Economics*, vol. 1, eds. Joseph P. Newhouse and Anthony J. Culyer. North-Holland.

Harvard

I searched the page <http://www.registrar.fas.harvard.edu/courses-exams/courses-instruction/economics> for the word “health,” finding five courses.

ECON 1389 Economics of Global Health (Margaret McConnell and Guenther Fink)

(no relevant items on syllabus)

ECON 1460 Economics of Health Care Policy (Joseph Newhouse)

Becker, Gary S., and Kevin M. Murphy. 1992. The Division of Labor, Co-ordination Costs, and Knowledge. *Quarterly Journal of Economics* 107(4): 1137-1160.

*Culyer, Anthony J., and Joseph P. Newhouse, eds. 2000. *Handbook of Health Economics*, vol. 1. North-Holland.

*Danzon, Patricia M., and Sean Nicholson, eds. 2012. *The Oxford Handbook of the Economics of the Biopharmaceutical Industry*. Oxford University Press.

*Folland, Sherman, Allen C. Goodman, and Miron Stano. 2012. *The Economics of Health and Health Care*, 7th ed. Prentice-Hall.

Fuchs, Victor R. 2011. *Who Shall Live?*, 3rd ed. World Scientific.

*Getzen, Thomas E. 2010. *Health Economics and Financing*, 4th ed. John Wiley & Sons.

*Morton, Fiona M. Scott, and Margaret Kyle. 2011. Markets for Pharmaceutical Products. In *Handbook of Health Economics*, vol. 2, eds. Mark V. Pauly, Thomas G. McGuire, and Pedro P. Barros, 763-823. North-Holland.

Parkin, David, John Appleby, and Alan Maynard. 2013. Economics: The Biggest Fraud Ever Perpetrated on the World? *Lancet*, October 2: e11-e15.

*Pauly, Mark V., Thomas G. McGuire, and Pedro Pita Barros, eds. 2012. *Handbook of Health Economics*, vol. 2. North-Holland.

*Phelps, Charles E. 2012. *Health Economics*, 5th ed. Prentice-Hall.

Rosenthal, Meredith B. 2009. What Works in Market-Oriented Health Policy? *New England Journal of Medicine* 360(21): 2157-2160.

*Scherer, F. M. 2000. The Pharmaceutical Industry. In *Handbook of Health Economics*, vol. 1, eds. Anthony J. Culyer and Joseph P. Newhouse, 1297-1336. North-Holland.

Sloan, Frank A., and Chee-Ruey Hsieh. 2008. The Effects of Incentives on Pharmaceutical Innovation. In *Incentives and Choice in Health Care*, eds. Frank A. Sloan and Hirschel Kasper, 228-262. MIT Press.

ECON 2395 Health and Social Justice

(new course; could not find instructor names or information on readings)

ECON 2465 Health Economics (David M. Cutler)

Budish, Eric, Benjamin N. Roin, and Heidi Williams. 2013. Do Fixed Patent Terms Distort Innovation?: Evidence from Cancer Clinical Trials. *NBER Working Paper* 19430. National Bureau of Economic Research.

Carpenter, Daniel. 2002. Groups, the Media, Agency Waiting Costs, and FDA Drug Approval. *American Journal of Political Science* 46(3): 490-505.

*Culyer, Anthony J., and Joseph P. Newhouse, eds. 2000. *Handbook of Health Economics*, vol. 1. North-Holland.

*Folland, Sherman, Allen C. Goodman, and Miron Stano. 2012. *The Economics of Health and Health Care*, 7th ed. Prentice-Hall.

*Morton, Fiona M. Scott, and Margaret Kyle. 2011. Markets for Pharmaceutical Products. In *Handbook of Health Economics*, vol. 2, eds. Mark V. Pauly, Thomas G. McGuire, and Pedro P. Barros, 763-823. North-Holland.

*Pauly, Mark V., Thomas G. McGuire, and Pedro Pita Barros, eds. 2012. *Handbook of Health Economics*, vol. 2. North-Holland.

Williams, Heidi. 2013. Intellectual Property Rights and Innovation: Evidence from the Human Genome. *Journal of Political Economy* 121(1): 1-27.

E&M-REASON 20 The Business and Politics of Health (David M. Cutler)

Cutler, David M. 2004. *Your Money or Your Life: Strong Medicine for America's Health Care System*. Oxford University Press.

*Folland, Sherman, Allen C. Goodman, and Miron Stano. 2012. *The Economics of Health and Health Care*, 7th ed. Prentice-Hall.

MIT

I searched for the word “health” in http://web.mit.edu/catalog/pdf/course_14.pdf, finding two courses.⁷⁸

14.21 Health Economics (Jeffrey Harris)

Azoulay, Pierre. 2002. Do Pharmaceutical Sales Respond to Scientific Evidence? *Journal of Economics and Management Strategy* 11(4): 551-593.

⁷⁸ I could not find either MIT course syllabus online, and I thank Jeffrey Harris and Heidi Williams for providing me with the necessary information from their course reading lists.

Iizuka, Toshiaki, and Ginger Zhe Jin. 2005. The Effect of Prescription Drug Advertising on Doctor Visits. *Journal of Economics and Management Strategy* 14(3): 701-727.

14.473 Public Policy in Health Economics (Amy Finkelstein, Jonathan Gruber, Heidi Williams)

Acemoglu, Daron, and Amy Finkelstein. 2008. Input and Technology Choices in Regulated Industries: Evidence from the Health Care Sector. *Journal of Political Economy* 116(5): 837-880.

Acemoglu, Daron, and Joshua Linn. 2004. Market Size in Innovation: Theory and Evidence from the Pharmaceutical Industry. *Quarterly Journal Of Economics* 119(3): 1049-1090.

Baker, Laurence C., and Ciaran S. Phibbs. 2002. Managed Care, Technology Adoption, and Health Care: The Adoption of Neonatal Intensive Care. *RAND Journal of Economics* 33(3): 524-548.

Budish, Eric, Benjamin Roin, and Heidi Williams. 2012. Do Fixed Patent Terms Distort Innovation? Evidence from Cancer Clinical Trials. Working paper.

*Carpenter, Daniel. 2010. *Reputation and Power: Organizational Image and Regulation at the FDA*. Princeton University Press.

Chandra, Amitabh, Anupam B. Jena, and Jonathan S. Skinner. 2011. The Pragmatist's Guide to Comparative Effectiveness Research. *Journal of Economic Perspectives* 25(2): 27-46.

Chandra, Amitabh, and Jonathan S. Skinner. 2011. Technology Growth and Expenditure Growth in Health Care. *NBER Working Paper* 16953. National Bureau of Economic Research.

Congressional Budget Office. 2008. Technological Change and the Growth of Health Care Spending. <http://www.cbo.gov/sites/default/files/cbofiles/ftpdocs/89xx/doc8947/01-31-techhealth.pdf>

*Culyer, Anthony J., and Joseph P. Newhouse, eds. 2000. *Handbook of Health Economics*, vol. 1. North-Holland.

- Cutler, David M. 2004. *Your Money or Your Life: Strong Medicine for America's Health Care System*. Oxford University Press.
- Cutler, David M. 2007. The Demise of the Blockbuster? *New England Journal of Medicine* 356(13): 1292-1293.
- Cutler, David M. 2008. Are We Finally Winning the War on Cancer? *Journal of Economic Perspectives* 22(4): 3-26.
- Cutler, David M. 2010. Where Are the Health Care Entrepreneurs? The Failure of Organizational Innovation in Health Care. *NBER Innovation Policy & The Economy* 11(1): 1-28.
- Cutler, David M., and Robert Huckman. 2003. Technological Development and Medical Productivity: The Diffusion of Angioplasty in New York State. *Journal of Health Economics* 22(2): 187-217.
- Dranove, David, and David Meltzer. 1994. Do Important Drugs Reach the Market Sooner? *RAND Journal of Economics* 25(3): 402-423.
- Duggan, Mark, and Fiona M. Scott Morton. 2006. The Distortionary Effects of Government Procurement: Evidence from Medicaid Prescription Drug Purchasing. *Quarterly Journal of Economics* 121(1): 1-31.
- Finkelstein, Amy. 2004. Static and Dynamic Effects of Health Policy. *Quarterly Journal Of Economics* 119(2): 527-567.
- Finkelstein, Amy. 2007. The Aggregate Effects of Health Insurance: Evidence from the Introduction of Medicare. *Quarterly Journal of Economics* 122(3): 1-37.
- Fuchs, Victor R. 2011. *Who Shall Live?*, 3rd ed. World Scientific.
- Garber, Alan M., and Mark J. Sculpher. 2011. Cost Effectiveness and Payment Policy. In *Handbook of Health Economics*, vol. 2, eds. Mark V. Pauly, Thomas G. McGuire, and Pedro P. Barros, 471-497. North-Holland.
- Goldman, Dana, and Darius Lakdawalla. 2011. Intellectual Property, Information Technology, Biomedical Research, and Marketing of Patented Products. In *Handbook of Health Economics*, vol. 2, eds. Mark V. Pauly, Thomas G. McGuire, and Pedro P. Barros, 825-872. North-Holland.
- Gruber, Jonathan. 2011. *Public Finance and Public Policy*, 3rd ed. Worth Publishers.

- Hemphill, C. Scott. 2006. Paying for Delay: Pharmaceutical Patent Settlement as a Regulatory Design Problem. *New York University Law Review* 81(1553): 101-167.
- Kremer, Michael, and Rachel Glennerster. 2004. *Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases*. Princeton University Press.
- Kremer, Michael, and Christopher M. Snyder. 2003. Why Are Drugs More Profitable Than Vaccines? *NBER Working Paper* 9833. National Bureau of Economic Research.
- Lee, Thomas H., and James Mongan, eds. 2009. *Chaos and Organization in Health Care*. MIT Press.
- *Malani, Anup, and Tomas Philipson. 2012. The Welfare Effects of FDA Regulation of Drugs. In *The Oxford Handbook of the Economics of the Biopharmaceutical Industry*, eds. Patricia Danzon and Sean Nicholson, 100-142. Oxford University Press.
- Meltzer, David O., and Peter C. Smith. 2011. Theoretical Issues Relevant to the Economic Evaluation of Health Technologies. In *Handbook of Health Economics*, vol. 2, eds. Mark V. Pauly, Thomas G. McGuire, and Pedro P. Barros, 433-469. North-Holland.
- Morton, Fiona M. Scott. 1999. Entry Decisions in the Generic Pharmaceutical Industry. *RAND Journal of Economics* 30(3): 421-440.
- *Morton, Fiona M. Scott, and Margaret Kyle. 2011. Markets for Pharmaceutical Products. In *Handbook of Health Economics*, vol. 2, eds. Mark V. Pauly, Thomas G. McGuire, and Pedro P. Barros, 763-823. North-Holland.
- Newhouse, Joseph P. 1992. Medical Care Costs: How Much Welfare Loss? *Journal Of Economic Perspectives* 6(3): 3-21.
- *Pauly, Mark V., Thomas G. McGuire, and Pedro Pita Barros, eds. 2012. *Handbook of Health Economics*, vol. 2. North-Holland.
- *Peltzman, Sam. 1973. An Evaluation of Consumer Protection Legislation: The 1962 Drug Amendments. *Journal Of Political Economy* 81(5): 1049-1091.
- Philipson, Tomas, Ernst Berndt, Adrian Gottschalk, and Eric Sun. 2008. Cost-Benefit Analysis of the FDA: The Case of the Prescription Drug User Fee Acts. *Journal of Public Economics* 92(5-6): 1306-1325.
- Rawlins, Michael D. 2004. NICE Work—Providing Guidance to the British National Health Service. *New England Journal of Medicine* 351(14): 1383-1385.

Sampat, Bhaven N., and Frank R. Lichtenberg. 2011. What are the Respective Roles of the Public and Private Sectors in Pharmaceutical Innovation? *Health Affairs* 30(2): 332-339.

*Scherer, F. M. 2000. The Pharmaceutical Industry. In *Handbook of Health Economics*, vol. 1, eds. Anthony J. Culyer and Joseph P. Newhouse, 1297-1336. North-Holland.

Scotchmer, Suzanne. 2004. *Innovation and Incentives*. MIT Press.

Skinner, Jonathan, and Douglas Staiger. 2009. Technology Diffusion and Productivity Growth in Health Care. *NBER Working Paper* 14865. National Bureau of Economic Research.

Thomas, Lacy Glenn. 1990. Regulation and Firm Size: FDA Impacts on Innovation. *RAND Journal of Economics* 21(4): 497-517.

Weisbrod, Burton A. 1991. The Health Care Quadrilemma: An Essay on Technological Change, Insurance, Quality of Care, and Cost Containment. *Journal of Economic Literature* 29(2): 523-552.

Welch, H. Gilbert. 2004. *Should I Be Tested for Cancer? Maybe Not and Here's Why*. University of California Press.

Williams, Heidi. 2012. Intellectual Property Rights and Innovation: Evidence from the Human Genome. Working paper.

Yin, Wesley. 2008. Market Incentives and Pharmaceutical Innovation. *Journal of Health Economics* 27: 1060-1077.

Zuckerman, Diana, Paul Brown, and Steven Nissen. 2011. Medical Device Recalls and the FDA Approval Process. *Archives of Internal Medicine* 171(11): 1006-1011.

York

I searched for the word “health” in <http://www.york.ac.uk/economics/current-students/ug-information/undergraduates2013-2016/#tab-2>, finding one course.

ECO00006H Health Economics (Luigi Siciliani)

*Culyer, Anthony J., and Joseph P. Newhouse, eds. 2000. *Handbook of Health Economics*, vol. 1. North-Holland.

Drummond, Michael F., Mark J. Sculpher, George W. Torrance, Bernie J. O'Brien, and Greg L. Stoddart. 2005. *Methods for the Economic Evaluation of Health Care Programmes*, 3rd ed. Oxford University Press.

*Folland, Sherman, Allen C. Goodman, and Miron Stano. 2009. *The Economics of Health and Health Care*, 6th ed. Prentice-Hall.

*Glied, Sherry, and Peter C. Smith, eds. 2011. *The Oxford Handbook of Health Economics*. Oxford University Press.

Jones, Andrew M., ed. 2012. *The Elgar Companion to Health Economics*, 2nd ed. Edward Elgar.

*Pauly, Mark V., Thomas G. McGuire, and Pedro Pita Barros, eds. 2012. *Handbook of Health Economics*, vol. 2. North-Holland.

Zweifel, Peter, Friedrich Breyer, and Mathias Kifmann. 2009. *Health Economics*, 2nd ed. Springer.

George Mason

I searched the Internet, using Google.com, for [GMU health economics syllabus], finding one course.

ECON 496 Health Economics (Robin Hanson)

Brownlee, Shannon. 2007. *Overtreated*. Bloomsbury.

*Folland, Sherman, Allen C. Goodman, and Miron Stano. 2009. *The Economics of Health and Health Care*, 6th ed. Prentice-Hall.

*Phelps, Charles E. 2003. *Health Economics*, 3rd ed. Addison Wesley.

Texas

I searched for “health” in <http://www.utexas.edu/cola/depts/economics/courses/>, finding two courses.

ECO 330T Health Economics (Helen Schneider)

The Economist. 2014. The New Drugs War. *The Economist*, January 4.

Hutton, John, Michael Borowitz, Inga Oleksy, and Bryan R. Luce. 1994. The Pharmaceutical Industry and Health Reform: Lessons from Europe. *Health Affairs* 13(3): 98-111.

*Phelps, Charles E. 2012. *Health Economics*, 5th ed. Prentice-Hall.

ECO 350K Health Economics (Helen Schneider)

*Folland, Sherman, Allen C. Goodman, and Miron Stano. 2012. *The Economics of Health and Health Care*, 7th ed. Prentice-Hall.

REFERENCES

- Agrawal, Shantanu (2014). "Open Payments Data Collection Moves Forward." *CMS Blog* (Centers for Medicare & Medicaid Services), May 22.
<http://blog.cms.gov/2014/05/22/open-payments-data-collection-moves-forward/>
- Akerlof, George A. (1970). "The Market for 'Lemons': Quality Uncertainty and the Market Mechanism." *Quarterly Journal of Economics* 84(3): 488-500.
- Alexander, Michelle (2010). *The New Jim Crow: Mass Incarceration in the Age of Colorblindness*. New York: New Press.
- Allais, Maurice (1953). "Le Comportement de l'Homme Rationnel Devant le Risque: Critique des Postulats et Axiomes de l'Ecole Americaine." *Econometrica* 21: 503-546.
- Angell, Marcia (2004). *The Truth About the Drug Companies: How They Deceive Us and What to Do About It*. New York: Random House.
- Armstrong, David (2003). "How Drug Directory Helps Raise Tab for Medicaid and Insurers." *Wall Street Journal*, October 23: A1.
- Arrow, Kenneth J. (1963). "Uncertainty and the Welfare Economics of Medical Care." *American Economic Review* 53: 941-973.
- Asch, David A., Jonathan Baron, John C. Hershey, Howard Kunreuther, Jacqueline Meszaros, Ilana Ritov, and Mark Spranca (1994). "Omission Bias and Pertussis Vaccination." *Medical Decision Making* 14: 118-123.
- Avorn, Jerry (2004). *Powerful Medicines: The Benefits, Risks, and Costs of Prescription Drugs*. New York: Alfred A. Knopf.
- Avorn, Jerry (2007). "In Defense of Pharmacoepidemiology—Embracing the Yin and Yang of Drug Research." *New England Journal of Medicine* 357: 2219-2221.
- Bar-Gill, Oren, and Elizabeth Warren (2008). "Making Credit Safer." *University of Pennsylvania Law Review* 157(1): 1-101.

Baron, Jonathan (1992). "The Effect of Normative Beliefs on Anticipated Emotions." *Journal of Personality and Social Psychology* 63: 320-330.

Baron, Jonathan, Jane Beattie, and John C. Hershey (1988). "Heuristics and Biases in Diagnostic Reasoning: II. Congruence, Information, and Certainty." *Organizational Behavior and Human Decision Processes* 42: 88-110.

Briggeman, Jason, Daniel B. Klein, and Kevin D. Rollins (2010a). "44 Transcripts: Economists Who Answered the Questionnaire on the Pre-Market Approval of Drugs and Devices." *Econ Journal Watch* 7(2): A1-A124.

Briggeman, Jason, Daniel B. Klein, and Kevin D. Rollins (2010b). "44 Economists Answer Questionnaire on the Pre-Market Approval of Drugs and Devices." *Econ Journal Watch* 7: 162-173.

Brownlee, Shannon (2008). *Overtreated: Why Too Much Medicine Is Making Us Sicker and Poorer*. New York: Bloomsbury.

Brynnner, Rock, and Trent Stephens (2001). *Dark Remedy: The Impact of Thalidomide and Its Revival As a Vital Medicine*. Cambridge, Mass.: Perseus Publishing.

Buchanan, Allen E. (2000). "Trust in Managed Care Organizations." *Kennedy Institute of Ethics Journal* 10(3): 189-212.

Buchanan, James M. (1975). *The Limits of Liberty: Between Anarchy and Leviathan*. University of Chicago Press.

Buchanan, James M. (2005). "Afraid to Be Free: Dependency as Desideratum." *Public Choice* 124: 19-31.

Budish, Eric, Benjamin N. Roin, and Heidi Williams (2013). "Do Firms Underinvest in Long-Term Research?: Evidence from Cancer Clinical Trials." *NBER Working Paper* 19430. National Bureau of Economic Research (Cambridge, Mass.).

Bursztajn, Harold, Benzion Chanowitz, Eric Kaplan, Thomas G. Gutheil, Robert M. Hamm, and Victoria Alexander (1991). "Medical and Judicial Perceptions of the Risks Associated with Use of Antipsychotic Medication." *Bulletin of the American Academy of Psychology and the Law* 19: 271-275.

Caplan, Bryan (2007). *The Myth of the Rational Voter: Why Democracies Choose Bad Policies*. Princeton University Press.

Carpenter, Daniel (2005). "A Simple Model of Placebo Learning with Self-Remitting Diseases." Unpublished paper.

Carpenter, Daniel (2009a). "Particulars of a Financial Product Safety Commission." In *Considering a Financial Product Safety Commission*, 8-10. Tobin Project, Inc. (Cambridge, Mass.).

Carpenter, Daniel (2009b). "Proposal for a Financial Product Approval Process with Modified File-And-Use Elements, Public Scrutiny, and Committed Experimentation." Working paper. <http://people.hmdc.harvard.edu/~dcarpent/finreg/file&use-carpenterproposal2009.pdf>

Carpenter, Daniel (2009c). "Confidence Games: How Does Regulation Constitute Markets?" In *Towards a New Theory of Regulation*, eds. Edward Balleisen and David Moss, 164-190. New York: Cambridge University Press.

Carpenter, Daniel (2010). *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA*. Princeton University Press.

Carpenter, Daniel, Justin Grimmer, and Eric Lomazoff (2010). "Approval Regulation and Endogenous Consumer Confidence: Theory and Analogies to Licensing, Safety, and Financial Regulation." *Regulation & Governance* 4: 383-407.

Carpenter, Daniel, and Michael M. Ting (2007). "Regulatory Errors with Endogenous Agendas." *American Journal of Political Science* 51(4): 835-852.

Centers for Medicare & Medicaid Services (2010). *Medicare Prescription Drug Benefit Manual*. Publication 100-18. http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/Pub100_18.pdf

Centers for Medicare & Medicaid Services (2012). "Information on Implementation of the Physician Payments Sunshine Act." *CMS Blog* (Centers for Medicare & Medicaid Services), May 3. <http://blog.cms.gov/2012/05/03/information-on-implementation-of-the-physician-payments-sunshine-act/>

Clark, A. J. (1937). "Individual Variation in Response to Drugs." *British Medical Journal* 2(3997): 307-310.

Coase, Ronald H. (1960). "The Problem of Social Cost." *Journal of Law and Economics* 3(Oct.): 1-44.

Collet, Jean-Paul (2000). "Limite des Essais Cliniques." *Revue du Praticien* 50: 833-837.

Cramer, Joyce A., Anuja Roy, Anita Burrell, et al. (2008). "Medication Compliance and Persistence: Terminology and Definitions." *Value in Health* 11: 44-47.

Craswell, Richard, and John E. Calfee (1986). "Deterrence and Uncertain Legal Standards." *Journal of Law, Economics, and Organization* 2(2): 279-303.

Crawford, Vincent P., and Joel Sobel (1982). "Strategic Information Transmission." *Econometrica* 50(6): 1431-1451.

Culyer, Anthony J., and Joseph P. Newhouse, eds. (2000). *Handbook of Health Economics*, vols. 1A and 1B. Amsterdam: North-Holland.

Cutler, David, Amy Finkelstein, and Kathleen McGarry (2008). "Preference Heterogeneity and Insurance Markets: Explaining a Puzzle of Insurance." *American Economic Review* 98: 157-162.

Danzon, Patricia M. (2011). "The Economics of the Biopharmaceutical Industry." In *The Oxford Handbook of Health Economics*, eds. Sherry Glied and Peter C. Smith, 520-554. Oxford: Oxford University Press.

Danzon, Patricia M., and Eric L. Keuffel (2007). "Regulation of the Pharmaceutical-Biotechnology Industry." Paper prepared for the NBER Conference on Regulation, September 2005; rev. September 12, 2007. http://www.nber.org/books_in_progress/econ-reg/danzon-keuffel9-14-07.pdf

Danzon, Patricia M., and Eric L. Keuffel (2014). "Regulation of the Pharmaceutical-Biotechnology Industry." In *Economic Regulation and Its Reform: What Have We Learned?*, ed. Nancy L. Rose, 407-484. Chicago: University of Chicago Press.

Darby, Michael R., and Edi Karni (1973). "Free Competition and the Optimal Amount of Fraud." *Journal of Law and Economics* 16(1): 67-88.

Das, Jishnu (2001). *Three Essays on the Provision and Use of Services in Low-Income Countries*. Ph.D. dissertation, Harvard University (Cambridge, Mass.).

David, Guy, Sara Markowitz, and Seth Richards-Shubik (2010). The Effects of Pharmaceutical Marketing and Promotion on Adverse Drug Events and Regulation. *American Economic Journal: Economic Policy* 2(4): 1-25.

Davis, William L., Bob G. Figgins, David Hedengren, and Daniel B. Klein (2011). "Economics Professors' Favorite Economic Thinkers, Journals, and Blogs (Along With Party and Policy Views)." *Econ Journal Watch* 8(2): 126-146.

Demsetz, Harold (1969). "Information and Efficiency: Another Viewpoint." *Journal of Law and Economics* 12(1): 1-22.

Devins, Neal (1993). "Political Will and the Unitary Executive: What Makes an Independent Agency Independent?" *Cardozo Law Review* 15: 273-312.

Dwyer, Jim (2009). "Whites Smoke Pot, But Blacks Are Arrested." *New York Times*, December 22.

Eisenberg, David M., Roger B. Davis, Susan L. Ettner, Scott Appel, Sonja Wilkey, Maria Van Rompay, and Ronald C. Kessler (1998). "Trends in Alternative Medicine Use in the United States, 1990–1997: Results of a Follow-up National Survey." *Journal of the American Medical Association* 280(18): 1569-1575. Link

Eisenberg, Rebecca S. (2005). "The Problem of New Uses." *Yale Journal of Health Policy, Law, and Ethics* 5(2): 717-740.

Emanuel, Ezekiel J., Trudo Lemmens, and Carl Elliott (2006). "Should Society Allow Research Ethics Boards to Be Run As For-Profit Enterprises?" *PLoS Medicine* 3(7): e309.

Eschenbach, Andrew von (2012). "Toward a 21st-Century FDA." *Wall Street Journal*, April 16: A15.

FDA.gov (2010a). "Questions and Answers about Avastin." December 16.
<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm237095.htm>

FDA.gov (2010b). "Coverage of Personal Importations." Section 9-2 in *Regulatory Procedures Manual*. February 16.
<http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm179266.htm>

FDA.gov (2011). "White Oak Campus Information: Project Schedule."
<http://www.fda.gov/AboutFDA/WorkingatFDA/BuildingsandFacilities/WhiteOakCampusInformation/ucm057328.htm>

Feldman, Martha S., and James G. March (1981). "Information in Organizations As Signal and Symbol." *Administrative Science Quarterly* 26: 171-186.

Finkelstein, Amy, Matthew Gentzkow, and Heidi Williams (2014). "Sources of Geographic Variation in Health Care: Evidence from Patient Migration." *NBER Working Paper* 20789. National Bureau of Economic Research (Cambridge, Mass.).

Flanigan, Jessica (2012). *Liberal Medicine*. Ph.D. dissertation, Department of Politics, Princeton University.

Fleischhacker, Sheila, and Mark Cohen (2009). "The ABCs of Drug Safety: Accountability, Balance, and Citizen Empowerment." Government Accountability Project (Washington, D.C.).

Folland, Sherman, Allen C. Goodman, and Miron Stano (2007). *The Economics of Health and Health Care*, 5th ed. Upper Saddle River, N.J.: Pearson Prentice Hall.

Food and Drug Administration Transparency Task Force (FDA TTF) (2010). "FDA Transparency Initiative: Draft Proposals for Public Comment Regarding Disclosure Policies of the U.S. Food and Drug Administration."
<http://www.fda.gov/AboutFDA/Transparency/PublicDisclosure/default.htm>

Frank, Sue A., and Gregory B. Lewis (2004). "Government Employees: Working Hard or Hardly Working?" *American Review of Public Organization* 34: 36-51.

Freemantle, Nick (2001). "Interpreting the Results of Secondary End Points and Subgroup Analyses in Clinical Trials: Should We Lock the Crazy Aunt in the Attic?" *British Medical Journal* 322: 989-991.

Fuchs, Victor R. (1974). *Who Shall Live?: Health, Economics, and Social Choice*. New York: Basic Books.

Gagne, Joshua J., and Niteesh K. Choudhry (2011). "How Many 'Me-Too' Drugs Is Too Many?" *Journal of the American Medical Association* 305(7): 711-712.

Gale, E. A. M. (2009). "Collateral Damage: The Conundrum of Drug Safety." *Diabetologia* 52: 1975-1982.

General Medical Convention (1820). *The Pharmacopoeia of the United States of America*. Boston: Wells and Lilly.

Getzen, Thomas E. (2010). *Health Economics and Financing*, 4th ed. Hoboken, N.J.: John Wiley & Sons.

Gieringer, Dale H. (1985). "The Safety and Efficacy of New Drug Approval." *Cato Journal* 5: 177-201.

Glaeser, Edward, and Andrei Shleifer (2003). "The Rise of the Regulatory State." *Journal of Economic Literature* 41: 401-425.

- Gutwillig, Stephen (2009). "The Racism of Marijuana Prohibition." *Los Angeles Times*, September 7.
- Hanson, Robin (2003). "Warning Labels as Cheap-Talk: Why Regulators Ban Drugs." *Journal of Public Economics* 87: 2013-2029.
- Hanson, Robin (2008). "Making Sense of Medical Paternalism." *Medical Hypotheses* 70: 910-913.
- Hare, R. M. (1981). *Moral Thinking: Its Levels, Method and Point*. Oxford: Oxford University Press.
- Harper, Andrew R., and Eric J. Topol (2012). "Pharmacogenomics in Clinical Practice and Drug Development." *Nature Biotechnology* 30(11): 1117-1124.
- Harrar, Sari (2009). "Are You Taking Unsafe Prescription Drugs?" *O, The Oprah Magazine*, June.
- Harris, Gardiner (2011). "Plan to Widen Availability of Morning-After Pill Is Rejected." *New York Times*, December 7.
- Harris, Gardiner (2012). "White House and F.D.A. at Odds on Regulatory Issues." *New York Times*, April 2.
- Harris, Richard (1964). *The Real Voice*. New York: Macmillan.
- Healy, David (2012). *Pharmageddon*. Berkeley, Calif.: University of California Press.
- Higgs, Robert (1994). "Banning a Risky Product Cannot Improve Any Consumer's Welfare (Properly Understood), with Applications to FDA Testing Requirements." *Review of Austrian Economics* 7(2): 3-20.
- Hinchey, Maurice R. (2005). Comment on "Prescription Drug User Fee Act (PDUFA): Public Meeting." *Regulations.gov*. Document ID No. FDA-2005-N-0099-0003. November 14.
- Hoffmann, Tammy C., and Chris Del Mar (2015). "Patients' Expectations of the Benefits and Harms of Treatments, Screening, and Tests: A Systematic Review." *JAMA Internal Medicine* 175(2): 274-286.
- Holston, Sharon S. (1996). "FDA Headquarters Consolidation Project." Statement before the Subcommittee on Public Buildings and Economic Development, House Committee

on Transportation and Infrastructure. May 23.

<http://www.fda.gov/NewsEvents/Testimony/ucm115078.htm>

Jefferson, Tom, Peter Doshi, Matthew Thompson, and Carl Heneghan (2011). "Ensuring Safe and Effective Drugs: Who Can Do What It Takes?" *British Medical Journal* 342: c7258.

Junod, Valerie (2004). "Drug Marketing Exclusivity Under United States and European Union Law." *Food and Drug Law Journal* 59: 479-518.

Kagan, Elena (2001). "Presidential Administration." *Harvard Law Review* 114: 2245-2385.

Kahneman, Daniel, and Amos Tversky (1979). "Prospect Theory: An Analysis of Decision Under Risk." *Econometrica* 47: 263-291.

Keller, L. Robin (1985). "The Effects of Problem Representation on the Sure-Thing and Substitution Principles." *Management Science* 31: 738-751.

Kent, David M., and Rodney A. Hayward (2007). "Limitations of Applying Summary Results of Clinical Trials to Individual Patients: The Need for Risk Stratification." *Journal of the American Medical Association* 298: 1209-1212.

Kesselheim, Aaron S., and Daniel H. Solomon (2010). "Incentives for Drug Development—The Curious Case of Colchicine." *New England Journal of Medicine* 362: 2045-2047.

Keynes, John Maynard (1923). *A Tract on Monetary Reform*. London: Macmillan.

Klein, Benjamin, and Keith B. Leffler (1981). "The Role of Market Forces in Assuring Contractual Performance." *Journal of Political Economy* 89: 615-641.

Klein, Daniel B. (1998a). "Quality-and-Safety Assurance: How Voluntary Social Processes Remedy Their Own Shortcomings." *Independent Review* 2(4): 537-555.

Klein, Daniel B. (1998b). "Liberty, Dignity, and Responsibility: The Moral Triad of a Good Society." In *3 Libertarian Essays*, 25-59. Irvington-on-Hudson, N.Y.: Foundation for Economic Education.

Klein, Daniel B. (2008). "Colleagues, Where Is the Market Failure? Economists on the FDA." *Econ Journal Watch* 5: 316-348.

Klein, Daniel B. (2012a). "The Forsaken-Liberty Syndrome: Looking at Published Judgments to Say Whether Economists Reach a Conclusion." *American Journal of Economics and Sociology* 71(5): 1250-1272.

Klein, Daniel B. (2012b). *Knowledge and Coordination: A Liberal Interpretation*. Oxford: Oxford University Press.

Klein, Daniel B., and Jason Briggeman (2010) (K&B). "305 Economists Called to Answer Questionnaire on the Pre-Market Approval of Drugs and Devices." *Econ Journal Watch* 7: 99-106.

Klein, Daniel B., and Stewart Dompe (2007). "Reasons for Supporting the Minimum Wage: Asking Signatories of the 'Raise the Minimum Wage' Statement." *Econ Journal Watch* 4: 125-167.

Klein, Daniel B., and Charlotta Stern (2007). "Is There a Free-Market Economist in the House? The Policy Views of American Economic Association Members." *American Journal of Economics and Sociology* 66: 309-334.

Klein, Daniel B., and Alexander Tabarrok (2008). "Do Off-Label Drug Practices Argue Against FDA Efficacy Requirements? A Critical Analysis of Physicians' Argumentation for Initial Efficacy Requirements." *American Journal of Economics and Sociology* 67: 743-775.

Koppl, Roger (2010). "The Social Construction of Expertise." *Society* 47: 220-226.

Kremers, Edward, and George Urdang (1976). *History of Pharmacy*, 4th ed., ed. Glenn Sonnedecker. Philadelphia: J. B. Lippincott.

Krumholz, Harlan M., Joseph S. Ross, Amos H. Presler, and David S. Egilman (2007). "What Have We Learnt from Vioxx?" *British Medical Journal* 334: 120-123.

Landefeld, J. Steven, Eugene P. Seskin, and Barbara M. Fraumeni (2008). "Taking the Pulse of the Economy: Measuring GDP." *Journal of Economic Perspectives* 22: 193-216.

Lasser, Karen E., Paul D. Allen, Steffie J. Woolhandler, David U. Himmelstein, Sidney M. Wolfe, and David H. Bor (2002). "Timing of New Black Box Warnings and Withdrawals for Prescription Medications." *Journal of the American Medical Association* 287: 2215-2220.

Lauer, Michael S., and Eric J. Topol (2003). "Clinical Trials—Multiple Treatments, Multiple End Points, and Multiple Lessons." *Journal of the American Medical Association* 289: 2575-2577.

- Law, Marc T. (2004). "History of Food and Drug Regulation in the United States." In *EH.Net Encyclopedia*, ed. Robert Whaples. <http://eh.net/encyclopedia/article/Law.Food.and.Drug.Regulation>
- Law, Marc T. (2011). "Food and Drug Regulation." In *Governing America: Major Decisions of Federal, State, and Local Governments from 1789 to the Present*, eds. Paul J. Quirk and William E. Cunio, 126-131. New York: Facts on File.
- Leland, Hayne (1979). "Quacks, Lemons and Licensing: A Theory of Minimum Quality Standards." *Journal of Political Economy* 87(6): 128-146.
- Levine, Harry G., and Deborah Peterson Small (2008). *Marijuana Arrest Crusade: Racial Bias and Police Policy in New York City 1997-2007*. New York: New York Civil Liberties Union.
- Lin, Jiunn H. (2007). "Pharmacokinetic and Pharmacodynamic Variability: A Daunting Challenge in Drug Therapy." *Current Drug Metabolism* 8: 109-136.
- Lindstrom, Laura J. (2002). "Reproduction in the Genetic Age: A Proposed Scheme for the Regulation of Assisted Reproductive Technologies." *Harvard Law School Student Papers*. <http://nrs.harvard.edu/urn-3:HUL.InstRepos:8846770>
- Lipsey, R. G., and Kelvin Lancaster (1956). "The General Theory of Second Best." *Review of Economic Studies* 24: 11-32.
- Lu, Anthony Y. H. (1998). "Drug-Metabolism Research Challenges in the New Millennium: Individual Variability in Drug Therapy and Drug Safety." *Drug Metabolism and Disposition* 26(12): 1217-1222.
- Madden, Bartley J. (2004). "Breaking the FDA Monopoly." *Regulation* 27(2): 64-66.
- Magat, Wesley A., and W. Kip Viscusi (1992). *Informational Approaches to Regulation*. Cambridge, Mass.: MIT Press.
- Malani, Anup, and Tomas Philipson (2012). "The Regulation of Medical Products." In *The Oxford Handbook of the Economics of the Biopharmaceutical Industry*, eds. Patricia M. Danzon and Sean Nicholson, 100-142. Oxford: Oxford University Press.
- Martindale, William, and W. Wynn Westcott (1883). *The Extra Pharmacopoeia of Unofficial Drugs and Chemical and Pharmaceutical Preparations*. London: H. K. Lewis.

McCluskey, Jill J. (2000). "A Game Theoretic Approach to Organic Foods: An Analysis of Asymmetric Information and Policy." *Agricultural and Resource Economics Review* 29(1): 1-9.

McGarity, Thomas O., and Sidney A. Shapiro (1980). "The Trade Secret Status of Health and Safety Testing Information: Reforming Agency Disclosure Policies." *Harvard Law Review* 93: 837-888.

Meyer, Robert J. (2004). "Potential Merits of Cannabinoids for Medical Uses." Statement before the Subcommittee on Criminal Justice, Drug Policy, and Human Resources, House Committee on Government Reform. April 1.
<http://www.fda.gov/NewsEvents/Testimony/ucm114741.htm>

Morgenson, Gretchen (2012). "How to Prevent a Financial Overdose." *New York Times*, March 31.

Morton, Fiona M. Scott, and Margaret Kyle (2011). "Markets for Pharmaceutical Products." In *Handbook of Health Economics*, vol. 2, eds. Mark V. Pauly, Thomas G. McGuire, and Pedro P. Barros, 763-823. Amsterdam: North-Holland.

Moynihan, Ray, Iona Heath, and David Henry (2002). "Selling Sickness: The Pharmaceutical Industry and Disease Mongering." *British Medical Journal* 324: 886-891.

Mulligan, Casey, and Andrei Shleifer (2005). "The Extent of the Market and the Supply of Regulation." *Quarterly Journal of Economics* 120: 1445-1473.

Mussa, Michael, and Sherwin Rosen (1978). "Monopoly and Product Quality." *Journal of Economic Theory* 18: 301-317.

Nardinelli, Clark (2014). Email correspondence with Jason Briggeman, June 3.

Navathe, Amol, and Guy David (2009). "The Formation of Peer Reputation among Physicians and Its Effect on Technology Adoption." *Journal of Human Capital* 3: 289-322.

Omarova, Saule T. (2012). "License to Deal: Mandatory Approval of Complex Financial Products." *Washington University Law Review* 90(1): 63-140.

Ornstein, Charles, Tracy Weber, and Dan Nguyen (2011). "Piercing the Veil, More Drug Companies Reveal Payments to Doctors." *ProPublica*, September 7.
<http://www.propublica.org/article/piercing-the-veil-more-drug-companies-reveal-payments-to-doctors>

Pauly, Mark V., Thomas G. McGuire, and Pedro Pita Barros (2012). *Handbook of Health Economics*, vol. 2. Amsterdam: North-Holland.

Peltzman, Sam (1973). "An Evaluation of Consumer Protection Legislation: The 1962 Drug Amendments." *Journal of Political Economy* 81: 1049-1091.

Peltzman, Sam (1974). *Regulation of Pharmaceutical Innovation: The 1962 Amendments*. Washington, D.C.: American Enterprise Institute for Public Policy Research.

Peltzman, Sam (1987). "The Health Effects of Mandatory Prescriptions." *Journal of Law and Economics* 30: 207-238.

Phelps, Charles E. (2000). "Information Diffusion and Best Practice Adoption." In *Handbook of Health Economics*, vol. 1, eds. Anthony J. Culyer and Joseph P. Newhouse, 223-264. Amsterdam: North-Holland.

Phelps, Charles E. (2012). *Health Economics*, 5th ed. Upper Saddle River, N.J.: Prentice Hall.

Philipson, Tomas, Ernst Berndt, Adrian Gottschalk, and Eric Sun (2008). "Cost-Benefit Analysis of the FDA: The Case of the Prescription Drug User Fee Acts." *Journal of Public Economics* 92(5-6): 1306-1325.

Philipson, Tomas J., and Eric Sun (2007). "Estimating the Welfare Effects of Alternative Product Liability Regimes." Unpublished paper.

Philipson, Tomas J., and Eric Sun (2008). "Is the Food and Drug Administration Safe and Effective?" *Journal of Economic Perspectives* 22(1): 85-102.

Philipson, Tomas J., Eric Sun, and Dana Goldman (2010). "The Effects of Product Liability Exemption in the Presence of the FDA." In *Regulation vs. Litigation: Perspectives from Economics and Law*, ed. Daniel P. Kessler, 137-163. Chicago: University of Chicago Press.

Philipson, Tomas J., Eric Sun, Anupam B. Jena, and Dana Goldman (2012). "A Re-Examination of the Costs of Medical R&D Regulation." *Forum for Health Economics and Policy* 15(2): 1-28.

Piketty, Thomas (2014). "Thomas Piketty Doesn't Hate Capitalism: He Just Wants to Change It" [interview by Matthew Yglesias]. *Vox*, April 24.
<http://www.vox.com/2014/4/24/5643780/who-is-thomas-piketty>

Posner, Eric A., and E. Glen Weyl (2013). "An FDA for Financial Innovation: Applying the Insurable Interest Doctrine to Twenty-First-Century Financial Markets." *Northwestern University Law Review* 107(3): 1307-1357.

Reinhardt, Uwe E. (2007). "The Pharmaceutical Sector in Health Care." In *Pharmaceutical Innovation: Incentives, Competition, and Cost-Benefit Analysis in International Perspective*, eds. Frank A. Sloan and Chee-Ruey Hsieh, 25-53. Cambridge University Press.

Rothenberg, Jerome (1993). "Social Strategy and the Tactics in the Search for Safety." *Critical Review* 7: 159-180.

Rothschild, Michael, and Joseph Stiglitz (1976). "Equilibrium in Competitive Insurance Markets: An Essay on the Economics of Imperfect Information." *Quarterly Journal of Economics* 90: 630-649.

Satia-Abouta, Jessie, Alan R. Kristal, Ruth E. Patterson, Alyson J. Littman, Kayla L. Stratton, and Emily White (2003). "Dietary Supplement Use and Medical Conditions: The VITAL Study." *American Journal of Preventive Medicine* 24: 43-51.

Scherer, F. M. (2000). "The Pharmaceutical Industry." In *Handbook of Health Economics*, vol. 1, eds. Anthony J. Culyer and Joseph P. Newhouse, 1297-1336. Amsterdam: North-Holland.

Sebelius, Kathleen (2011). Memorandum to Margaret A. Hamburg, M.D., Commissioner of Food and Drugs. Department of Health and Human Services (Washington, D.C.), December 7. <http://www.hhs.gov/news/press/2011pres/12/20111207a.pdf>

Shafir, Eldar (1993). "Choosing Versus Rejecting: Why Some Options Are Both Better and Worse Than Others." *Memory & Cognition* 21: 546-556.

Shapiro, Carl (1983). "Premiums for High Quality Products as Returns to Reputations." *Quarterly Journal of Economics* 98: 659-680.

Shapiro, Carl (1986). "Investment, Moral Hazard, and Occupational Licensing." *Review of Economic Studies* 53: 843-862.

Shavell, Steven (1987). *Economic Analysis of Accident Law*. Cambridge, Mass.: Harvard University Press.

Shavell, Steven (2004). *Foundations of Economic Analysis of Law*. Cambridge, Mass.: Harvard University Press.

Slovic, Paul, and Amos Tversky (1974). "Who Accepts Savage's Axiom?" *Behavioral Science* 19: 368-373.

Smith, Adam (1776) [1976]. *An Inquiry into the Nature and Causes of the Wealth of Nations*. Eds. R. H. Campbell and A. S. Skinner. Oxford: Oxford University Press.

Smith, Adam (1790) [1976]. *The Theory of Moral Sentiments*. Eds. D. D. Raphael and A. L. Macfie. Oxford: Oxford University Press.

Smythe, James G. (2002). "Reputation, Public Information, and Physician Adoption of an Innovation." *European Journal of Health Economics* 3: 103-110.

Solow, Robert M. (2012). "The Serfdom Scare." *New Republic*, December 6.

Spence, Michael (1977). "Consumer Misperceptions, Product Failure and Producer Liability." *Review of Economic Studies* 44(3): 561-572.

Spranca, Mark, Elisa Minsk, and Jonathan Baron (1991). "Omission and Commission in Judgment and Choice." *Journal of Experimental Social Psychology* 27: 76-105.

Starr, Paul (1982). *The Social Transformation of American Medicine*. New York: Basic Books.

Tabarrok, Alexander T. (2000). "Assessing the FDA via the Anomaly of Off-Label Drug Prescribing." *Independent Review* 5: 25-53.

Thomas, Lacy Glenn (1990). "Regulation and Firm Size: FDA Impacts on Innovation." *RAND Journal of Economics* 21(4): 497-517.

Tirole, Jean (1988). *The Theory of Industrial Organization*. Cambridge, Mass.: MIT Press.

Tullock, Gordon (1995). "Thinking About Thought." *European Journal of Law and Economics* 2: 119-125.

Tuohy, Carolyn Hughes, and Sherry Glied (2011). "The Political Economy of Health Care." In *The Oxford Handbook of Health Economics*, eds. Sherry Glied and Peter C. Smith, 58-77. Oxford: Oxford University Press.

Tversky, Amos, and Daniel Kahneman (1981). "The Framing of Decisions and the Psychology of Choice." *Science* 211: 453-458.

Tversky, Amos, and Daniel Kahneman (1986). "Rational Choice and the Framing of Decisions." *Journal of Business* 59: S251-S278.

Tversky, Amos, and Daniel Kahneman (1992). "Advances in Prospect Theory: Cumulative Representation of Uncertainty." *Journal of Risk and Uncertainty* 5: 297-323.

Union of Concerned Scientists (2006). "Voices of Scientists at FDA: Protecting Public Health Depends on Independent Science." Union of Concerned Scientists (Cambridge, Mass.). http://www.ucsusa.org/assets/documents/scientific_integrity/fda-survey-brochure.pdf

Union of Concerned Scientists (2012). "Voices of Scientists at the FDA: Measuring Progress on Scientific Integrity." March. Union of Concerned Scientists (Cambridge, Mass.). http://www.ucsusa.org/assets/documents/scientific_integrity/fda-survey-report-2011.pdf

U.S. Senate. Committee on the Judiciary. Subcommittee on Antitrust and Monopoly (1961). *Administered Prices—Drugs*. 87th Congress, 1st Session, Report No. 448. Washington, D.C.: U.S. Government Printing Office.

Venning, G. R. (1982). "Validity of Anecdotal Reports of Suspected Adverse Drug Reactions: The Problem of False Alarms." *British Medical Journal* 284: 249-252.

Viner, Jacob (1927). "Adam Smith and Laissez-Faire." *Journal of Political Economy* 35: 198-232.

Wazana, Ashley (2000). "Physicians and the Pharmaceutical Industry: Is a Gift Ever Just a Gift?" *Journal of the American Medical Association* 283: 373-380.

Wennberg, John, and Alan Gittelsohn (1973). "Small Area Variations in Health Care Delivery." *Science* 182: 1102-1108.

Whittet, Douglas (1983). "One Hundred Years of Information on Drugs." *British Medical Journal* 286: 1032-1034.

Wildavsky, Aaron (1988). *Searching for Safety*. New Brunswick, N.J.: Transaction.

Wittman, Donald (1995). *The Myth of Democratic Failure: Why Political Institutions Are Efficient*. University of Chicago Press.

Wolfe, Sidney M. (2012). "The Seven-Year Rule for Safer Prescribing." *Australian Prescriber* 35(5): 138-139.

Wood, George B., and Franklin Bache (1833). *The Dispensatory of the United States of America*. Philadelphia: Grigg and Elliot.

Wood, Horatio C. Jr. (1931). "The History of the United States Dispensatory." *Journal of the American Pharmaceutical Association* 20(8): 791-794.

Young, James H. (1992). Afterword to *The Medical Messiahs: A Social History of Health Quackery in Twentieth-Century America*. Princeton University Press.

Zweifel, Peter, Friedrich Breyer, and Mathias Kifmann (2009). *Health Economics*, 2nd ed. Dordrecht, Netherlands: Springer.

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