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## Response

# Right Question, Wrong Answer: A Response to Professor Epstein and the “Permititis” Challenge

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### INTRODUCTION

Professor Epstein’s article<sup>1</sup> on FDA regulation of drugs forces us to think about life and death issues and personal freedom. It forces us to address a complex balance of competing and sometimes contradictory values, goals, and policies. We have come to expect no less from his writings. While he has asked the right question, I must respectfully dissent from his answer. His solution devalues the benefit of the government regulatory system, flies in the face of real-world experience, and cannot be implemented as he envisions.

The tragic story of Abigail Burroughs puts a very real and human face on what otherwise can sound like esoteric philosophical issues or regulatory nerds debating obscure (and Epstein might even say obscene) regulations. The short version of her story is as follows: Abigail Burroughs was diagnosed with cancer at age nineteen. Standard medical therapies failed. Her physicians concluded that her only chance to live was to try either of two new, experimental drugs. Neither drug was then FDA approved. As such, they were not available for her use and she didn’t qualify for any clinical trials. After a full disclosure of risks, she decided she wanted to try either of these drugs any-

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1. Richard A. Epstein, *Against Permititis: Why Voluntary Organizations Should Regulate the Use of Cancer Drugs*, 94 MINN. L. REV. 1 (2009). It is important to note that Epstein is not arguing that current law supports his position. Rather, he concedes that current law would need major revision in order to implement his concepts. *See id.* at 41. Given this approach, his article and this Response focus primarily on policy issues.

way—it was literally her last chance. Her doctors agreed with her decision. However, FDA regulations prevented her from gaining access to either drug. She died of cancer at age twenty-one.<sup>2</sup>

Ironically, the drugs she wanted were later approved by the FDA within months of her death. Whether they would have helped her will never be known. But FDA regulations deprived her of the chance to try a potentially lifesaving drug. Ms. Burroughs's story is a stark reminder that initial access to new drugs in the United States is currently controlled by the FDA, not the patient or physician, and that these decisions have life and death consequences.<sup>3</sup>

Epstein's article proposes a different answer; namely that Ms. Burroughs and her physicians, not the FDA, should have the right to make the decision regarding whether to use a particular therapy. The crux of Professor Epstein's proposal is that patients and voluntary professional medical organizations should make these decisions once very basic safety concerns (such as toxicology or pharmacology) have been assessed by the FDA.<sup>4</sup>

Under his construct, volunteer professional medical associations would assess overall drug efficacy and relative therapeutic efficacy between and among therapeutic options. This information would be translated into practice guidelines or other decision support tools to be used by the medical community, the individual doctor, and the patient to decide which drug to use.<sup>5</sup>

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2. See Our Story, <http://www.abigail-alliance.org/story.php> (last visited Apr. 13, 2010) (describing the facts surrounding the Abigail Burroughs story). See also the three key Abigail Alliance cases: *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, 495 F.3d 695 (D.C. Cir. 2007) (en banc), cert. denied, 128 S. Ct. 1069 (2008); *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, 445 F.3d 470 (D.C. Cir. 2006); and *Abigail Alliance for Better Access to Developmental Drugs v. McClellan*, No. 03-1601 (RMU), 2004 WL 3777340, at \*1 (D.D.C. Aug. 30, 2004). The policy arguments advanced by Epstein were largely argued and rejected by the D.C. Court of Appeals in the 2007 en banc decision. 495 F.3d at 703.

3. Epstein focuses on cancer drugs. He asserts that cancer drugs present the best case for government control given the risks of many cancer therapies. Epstein, *supra* note 1, at 4. From my perspective, cancer drugs may actually present the best argument for minimal government control given the critical nature of the disease, lack of therapeutic options, high levels of physician involvement, minimal risk to third parties and the need for prompt medical action.

4. *Id.* at 41.

5. *Id.* at 6–8.

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Policymakers and the FDA must, however, consider more than Abigail Burroughs. They must also consider the need to protect vulnerable patients from bad medicine and medical and economic fraud, and the need to promote scientifically accurate assessments of new therapies.

Epstein's position raises two broad sets of issues. The first set involves philosophical, legal, ethical, and policy issues. Should someone like Abigail Burroughs have the ultimate and essentially unregulated power to decide what drug to take?<sup>6</sup> What is the balance between personal choice and government protection, particularly with vulnerable populations? How do we address the charlatans, quack therapies, and snake oil salesmen preying on desperate people? If the government is to play a major role, then one must determine how, to what extent, and based on what factors.

After providing a brief history of FDA regulatory schemes in Part I, Part II addresses these issues, to which there are no easy answers. However, Epstein downplays the negative ramifications of an "open access" policy. When faced with these negatives, policymakers and the public have insisted on a (never perfect) balance between allowing access and protecting patients. It is important to understand that the current regulatory structure actually already provides significant access to unapproved drugs, thus moderating the impact of Epstein's policy concerns.

The second set of issues is more practical. Epstein's position requires accepting the fundamental and outcome-critical assumptions that the medical profession will develop the needed information in a reliable and timely fashion, practitioners will generally conform their medical practice to those determinations, and patients can and will understand the complex scientific information.

Parts III and IV set forth the crux of my disagreement with Epstein on these issues. We know from both history and an understanding of the current systems and structures that his proposed solution will not work as he intends it to. Even if one tends to agree with his philosophical points, his solution is impractical.

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6. As the concepts and issues are similar, I will not separately discuss biologics or medical devices except as relevant to illustrate some specific point.

There are serious issues with the slowness of current regulatory processes,<sup>7</sup> reduced patient autonomy, the FDA's impact in restricting patient choice, and the existing bottleneck on new therapies.<sup>8</sup> However, I respectfully dissent with regards to Epstein's proposed solution. Unaddressed policy issues and practical reality, both past and present, call into serious question whether the medical profession is capable of meeting this challenge or is even the appropriate body to assume this responsibility.

Currently, under the Federal Food Drug and Cosmetic Act,<sup>9</sup> the FDA must approve a "new drug"<sup>10</sup> before it can be distributed (whether for profit or not) in the United States outside of an FDA-approved clinical trial.<sup>11</sup> To be approved, the drug<sup>12</sup> must be shown to be "safe" and "effective" for its intended (or "labeled")<sup>13</sup> purpose.<sup>14</sup> Safety and efficacy must be established by well-controlled clinical studies<sup>15</sup> (usually multiple double-blind, placebo-controlled studies in the case of drugs). Generally, new drugs go through a three-part clinical testing schema. Phase I studies, designed to elicit basic safety data, are con-

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7. Epstein correctly differentiates issues of agency authority and power from issues regarding agency capabilities (funding, resources, political will, and so on). I will endeavor to follow his lead and focus on the fundamental authority/power questions.

8. Nothing in this commentary should be viewed as criticizing individual FDA employees or decisions. In my experience, the vast majority of FDA employees are conscientious individuals who care about public health.

9. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301–399 (2006).

10. *Id.* § 321(p) (defining "new drug"). New drugs must also go through a testing and approval process. *Id.* § 355. Section 355(a) requires an approved New Drug Application (NDA) prior to distribution. *Id.* § 355(a).

11. New drugs undergo clinical testing under the "Investigational New Drug" or IND process. 21 U.S.C. § 355(i) (2006 & Supp. 2009); 21 C.F.R. § 312 (2009) (explaining the requirements of IND applications for FDA approval).

12. 21 U.S.C. § 321(g) (2006) (defining "drug"). Epstein's article focuses on "drugs."

13. *Id.* § 321(m) (defining "labeling").

14. 21 U.S.C. § 355(c)–(d); 21 C.F.R. § 314. Note that neither "safety" nor "efficacy" is explicitly defined by statute. The same access issues can apply to biologics. *See* 42 U.S.C. § 262(a) (2006 & Supp. 2009) (providing that a biologics license shall be issued upon a sufficient demonstration that the product is safe); 21 C.F.R. § 601.2. Similar issues may arise regarding certain medical devices. *See* 21 U.S.C. § 360e; 21 C.F.R. § 814.2. The details may differ between these regulatory structures but the basic concepts and issues remain. As such we will focus on the drug provisions but acknowledge the existence of these other FDA regulatory systems.

15. *See* FOOD AND DRUG LAW AND REGULATION 323 (David G. Adams et al. eds., 2008).

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ducted on approximately 80–100 healthy volunteers. Phase II and III studies are conducted on larger groups of subjects with the disease or condition being studied, and assess both safety and efficacy. There are generally approximately 200–300 subjects in Phase II studies and often multiple thousands of patients enrolled in Phase III studies.<sup>16</sup> The Abigail Alliance and Epstein in essence argue that patients should have free access to the drug after the drug has successfully completed Phase I studies. Epstein proposes eliminating the FDA’s approval role once basic safety has been established via some form of Phase I studies. Professional medical and scientific societies would instead serve as the key information source for physicians. He contends that this approach would improve access to new drugs, decrease delays in access, and increase patient autonomy or control without exposing patients to any significant risks. He further contends that these voluntary professional organizations will provide better overall decisions and can respond faster than the FDA to new information.

Interestingly, once a drug is approved for any one purpose, a physician is generally free to use it for any other purpose.<sup>17</sup> This “off-label” use can actually be the standard of care. The irony of the Abigail Burroughs situation is that if the drug she wanted had been FDA-approved for some totally unrelated purpose—hair loss, acne, ingrown toenail—she could have gotten access without any FDA interference. This stark paradox certainly calls into question the public protection rationale used to support the current structure. If the FDA need not review and approve off-label uses before patient use, why must the FDA review on-label uses before allowing patient access? This paradox certainly supports Epstein’s criticism of the current structure.

His bottom line is that the current policy and the power balance between the individual and the state is wrong, and that we need substantially more patient autonomy and authority by moving the power to control access to new drugs from the government to the patient, physician, and professional societies. He contends that voluntary medical associations are better positioned than the FDA to collect therapeutic related data, particularly regarding rare diseases.<sup>18</sup> “A national (or even global) network [of voluntary associations] can better accumu-

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16. *Id.* at 326–27.

17. 21 U.S.C. § 396 (2006).

18. Epstein, *supra* note 1, at 29.

late information on rare diseases by publishing resources more rapidly than any federal agency."<sup>19</sup> In essence, he proposes a material reduction in the role of the FDA in favor of an increased role for the medical profession and companies. Specifically, he asserts, "The FDA's permit power is an open wound in the body politic . . . it should be eliminated."<sup>20</sup> He is clear that his position is an outlier.<sup>21</sup> Very few other commentators go as far as he does. He is one of the few to argue that: "The government-run FDA should step out of the approval and permit process—after the completion of Phase I clinical trials—thereby allowing decisions to rest in the hands of patients and their physicians."<sup>22</sup>

### I. PAST APPROACHES

Epstein is not the first to address the balance between patient autonomy and government control. A short history demonstrates that this balance varied over time.

*Pre-1906:* Before 1906, there was essentially no federal regulation of drugs. The balance was clearly tipped towards the patient who had essentially complete access.

*1906–1938:* The first Pure Food and Drug Act was passed in 1906. This Act did not include any premarket approval or control mechanisms, but made it illegal to distribute an "adulterated" or "misbranded" drug. During this time, the balance remained tilted towards patient autonomy—enforcement was after the fact and generally triggered by patient harm. This approach came under attack in the mid-1930s with the elixir of sulfanilamide tragedy in which several hundred individuals, including many children, died because of an antibiotic preparation that included diethylene glycol—a known poison.

*1938–1962:* In response to the sulfanilamide tragedy, in 1938 Congress passed the Food Drug and Cosmetic Act (FDCA),<sup>23</sup> giving the FDA the role of "gatekeeper" for approving "new drugs"<sup>24</sup> for distribution. Here we see the balance changing towards some (but not unlimited) government control over access, up to the point when safety (but not efficacy) was estab-

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19. *Id.*

20. *Id.* at 41.

21. *Id.* at 40.

22. *Id.* at 23.

23. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301–399 (2006).

24. *Id.* § 321(p) (prohibiting the introduction of new drugs into interstate commerce without first obtaining approval).

lished.<sup>25</sup> Then, in the early 1950s, statutory regulation of prescription (Rx) drugs was implemented, requiring a physician prescription for access to Rx drugs.<sup>26</sup> Under this system the physician is a key gatekeeper and part of a growing system to regulate access to drugs in the name of patient protection. In many ways, Epstein is proposing a return to the 1950–1962 era, when the FDA would review drugs for safety but not efficacy and then let patients, physicians, and professional societies decide from there.

*Post-1962:* In 1962, in response to another tragedy—this time regarding thalidomide—Congress created the current overall premarket approval structure (although there have been some important modifications since this date). The current structure requires the FDA to review a new drug for both safety and efficacy.<sup>27</sup> Clinical trials were carefully controlled and tremendous volumes of data had to be generated. The first years of this post-1962 period mark the apex of FDA control over access.

*1970s:* During this time, public attention began to focus on cancer and cancer treatments, and access issues started to become important policy issues. For example, in the 1970s a drug called laetrile got tremendous attention from cancer patients (and the media). Some claimed that it was the “magic bullet” against cancer. Unfortunately, the science did not bear out these claims. Despite the lack of scientific support, a number of people, demanded access to laetrile in the name of patient autonomy. The FDA refused to approve laetrile or to make it generally available. Multiple patients filed lawsuits asserting a right to access laetrile, culminating in the Supreme Court decision in *United States v. Rutherford*.<sup>28</sup> In *Rutherford*, the Court rejected arguments that the FDCA did not apply to drugs for terminal illnesses and upheld the FDA’s control over new drug approvals and access.<sup>29</sup>

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25. The statute has separate safety and efficacy provisions for historical reasons. There is no such thing as absolute safety (every drug has a side effect) or absolute efficacy. Separating these concepts does a disservice as safety can only be determined with reference to efficacy and vice versa. The agency and other stakeholders often use the risk/benefit language in lieu of safety and efficacy. This statutory disconnect between safety and efficacy is outside the scope of this paper but deserves attention.

26. 21 U.S.C. § 353(b).

27. 21 U.S.C. § 355(b) (2006 & Supp. 2009).

28. 442 U.S. 544 (1979).

29. *Id.* at 551–54.

*1980s:* In the 1980s, cancer and AIDS activists became increasingly critical of the FDA's role in limiting access to drugs for life-threatening conditions. Pressure from these groups led to a number of regulatory adjustments designed to speed access.<sup>30</sup> Congress also eased the regulatory pathway for drugs and devices intended to treat small populations (so-called orphan drugs) in an effort to increase product development and access.<sup>31</sup> This provided somewhat faster access for certain products, but did not eliminate much of the FDA's role as the gatekeeper.

*2000s:* In the current era, the Abigail Alliance case was the lightning rod in the ongoing battle to balance access with patient protection. The Abigail Alliance argued that there is a substantive due process right for terminally ill patients, with a physician prescription, to have access to experimental drugs that had completed Phase I testing—essentially the position advanced by Epstein. After a three-judge panel found in favor of the Abigail Alliance, the D.C. Court of Appeals rejected the substantive due process argument.<sup>32</sup> This remains the current state of the case law. However, the political pressure generated by this case helped push the FDA towards further regulatory changes intended to permit expanded access in limited circumstances.<sup>33</sup> In addition, the FDA now posts information online on how to get access to experimental drugs<sup>34</sup> and informa-

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30. See, e.g., 21 U.S.C. § 356 (2006 & Supp. 2009) (providing for a "fast track" approval process). Interestingly, the fast track process has some of the features argued for by Professor Epstein. There was also pressure on the FDA to increase its timeliness and actually meet the deadlines provided by statute. 21 U.S.C. § 355(c)(1) (2006) (imposing a 180-day deadline on the FDA to complete its review of a New Drug Application).

31. 21 U.S.C. §§ 360aa–360ee (2006 & Supp. 2009).

32. *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, 495 F.3d 695, 722–24 (D.C. Cir. 2007) (en banc), *cert. denied*, 128 S. Ct. 1069 (2008).

33. See U.S. FOOD & DRUG ADMIN., ACCESS TO INVESTIGATIONAL DRUGS, <http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/AccessToInvestigationalDrugs/default.htm> (last visited Apr. 13, 2010) (providing an overview of the FDA's approach towards access to investigational drugs). There have been some other more unusual and fact-specific access cases. See, e.g., *Gunvalson v. PTC Therapeutics, Inc.*, 303 F. App'x 128, 130 (3d Cir. 2008) (rejecting on factual grounds a promissory estoppel claim based on allegations that a company had promised a patient access to a later clinical trial if the patient did not seek entry into a more preliminary study).

34. See U.S. Food & Drug Admin., Access to Investigational Drugs Outside of a Clinical Trial, <http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/AccessToInvestigationalDrugs/ucm176098.htm> (last visited Apr. 13, 2010).

tion on all clinical trials underway.<sup>35</sup> While not unlimited, this access does provide some relief from the rigidity of the Investigational New Drug (IND) and New Drug Application (NDA) processes<sup>36</sup> and some level of enhanced access.

Changes in the regulatory system, particularly those since 1962, illustrate the search for the right balance between patient autonomy and public health. That balancing process continues—to the complete satisfaction of no one. By way of example, Representative Diane Watson recently introduced legislation to expand access to unapproved drugs.<sup>37</sup> Whether this legislation will actually result in change is unknown.

## II. THE POLICY DILEMMA

### A. THE TWO COMPETING INTERESTS

One cannot help but look at the Abigail Burroughs situation and lament her situation and her loss of autonomy. She was young, intelligent, and vibrant, had the counsel of the best doctors, and wanted a product that was a legitimate (and the only) option. If you were in her position, would you not demand access to the one drug that might save you?

Likewise, one cannot help but be worried about vulnerable cancer patients, desperate for any hope, who fall victim to medical fads, quacks, incomplete information, false cures, and outright fraud. Diverting public health care funds from legitimate treatment options to “miracle cures” creates real financial loss and represents a significant lost-opportunity cost. Valuable medical study and data collection opportunities go by the wayside. More importantly, patients may be bypassing better treatments based on false claims of miracle cures. The FDA recognizes that this is a real problem. As one FDA official explained, “[H]armful products [include] those that do not themselves cause injury, but may lead people to delay or reject proven remedies, possibly worsening their condition.”<sup>38</sup> One

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35. See *Clinicaltrials.gov*, <http://www.clinicaltrials.gov> (last visited Apr. 13, 2010).

36. 21 U.S.C. § 355(a), (i).

37. Compassionate Access Act of 2010, H.R. 4732, 111th Cong. (2010).

38. *Cancer Care for the New Millennium: Integrative Oncology: Hearing Before the H. Comm. on Government Reform*, 106th Cong. 76 (2000) (statement of Dr. Richard Pazdur, U.S. Food & Drug Admin.), [http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=106\\_house\\_hearings&docid=f:72932.pdf](http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=106_house_hearings&docid=f:72932.pdf).

FDA site alone identifies 187 current "fake cancer cures."<sup>39</sup> Desperate cancer patients are easy victims, and the FDA is charged by statute with preventing consumer fraud.<sup>40</sup>

Epstein discusses both "type I" errors (a product that causes harm) and "type II" errors (the harm caused by the lack of a therapy).<sup>41</sup> Approval decisions must (and the FDA argues already do) take into account both issues. Epstein's discussion of the risks of unapproved therapies downplays the problem of ineffective or fraudulent therapies,<sup>42</sup> focusing instead on "legitimate" experimental drugs. Unfortunately, that is not the real world, as there are many false or fraudulent cures being pushed on patients. His proposal would do little to limit the harm caused by these products.

As is always the case, each policy position, taken to its logical endpoint, leads to results that are seemingly unacceptable. Should the FDA have complete power to make life and death access decisions? That seems wrong. Should any patient, no matter how vulnerable, have the unfettered right to be duped by quacks and also lose the benefit of better therapeutic options? That also seems wrong.

#### B. THE SERIOUS POLICY RISKS INHERENT IN UNFETTERED ACCESS

Epstein's argument concentrates on the positives of enhanced access. He tees up, but does not fully analyze, the theoretical or conceptual conflict between the "right to die" and the "right to live" or, in his words, the "defensive" versus "offensive" view of autonomy.<sup>43</sup> More importantly, key countervailing policy issues are given minimal attention. Unfettered access to experimental drugs carries substantial risk to individuals and to public health.

##### 1. Protecting the Vulnerable

Terminally ill patients are at particular risk of being preyed upon by the unscrupulous or uninformed. Fraudulent

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39. U.S. Food & Drug Admin., 187 Fake Cancer "Cures" Consumers Should Avoid, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/ucm171057.htm> (last visited Apr. 13, 2010).

40. See 21 U.S.C. § 393(b) (2006) (charging the FDA with protecting the public health by ensuring that foods are properly labeled, for example).

41. See Epstein, *supra* note 1, at 9.

42. See *id.* at 19–20, 30.

43. See *id.* at 2.

cancer cures are a common scam.<sup>44</sup> Throughout the FDA's history, a key impetus for stricter drug regulation has been the financial and medical damage caused by people pushing quack remedies or advocating unscientific, ineffective "cures."

One need only look at history and at various FDA enforcement actions to confirm the obvious financial risks. Medical risks are also real. Certain doctors may have actually believed that laetrile was the magic bullet. By pushing laetrile these doctors kept patients from other legitimate therapies which may have worked and would have added to the universal knowledge of cancer. Thus, patients run the very real risk of suffering substantive physical harm from side effects, not getting any benefit, being diverted from more effective therapies, receiving false or incomplete information, and suffering substantial economic loss.

Epstein's proposal leaves these vulnerable populations open to greater exploitation in the name of autonomy. One way to justify the current system under Epstein's "liberal" view of government regulation would be if the current system does provide some meaningful "collateral gain in the quality and safety of medical decisions"<sup>45</sup> (and I would add economic protection). Such collateral gain exists, as exemplified by patients saved from the harms detailed above. Epstein implicitly recognizes that there are charlatans who will take advantage of terminally ill patients. His view is that strong, after-the-fact enforcement is the answer.<sup>46</sup> We tried this approach in the pre-1938 time frame and it proved unacceptable to the American people. There is no reason to believe that public opinion has changed.

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44. The FDA devotes a portion of its website to warning consumers about fraudulent cancer cures. U.S. FOOD & DRUG ADMIN., BEWARE OF ONLINE CANCER FRAUD 2 (July 17, 2008), <http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM143670.pdf>. The FDA has taken many enforcement actions against entities or individuals pushing fake cures. *See, e.g.*, News Release, U.S. Food & Drug Admin., FDA Warns Individuals and Firms to Stop Selling Fake Cancer Cures (June 17, 2008), *available at* <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116913.htm>; Letter from Susan J. Walker, M.D., Dir., Div. of Dietary Supplement Programs, Office of Nutritional Prods. Labeling & Dietary Supplements, Ctr. for Food Safety & Applied Nutrition to Michael Kellet, Health-Marketplace.com (Jan. 30, 2006), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/CyberLetters/ucm056388.pdf>.

45. Epstein, *supra* note 1, at 5.

46. *Id.* at 23–24.

One cannot blithely say that patients should have access to legitimate experimental therapies but not to nonlegitimate therapies. There is no way to universally separate "legitimate" experimental products from "quack" experimental products without some level of testing and oversight. The breakthrough therapy might be strongly questioned by the established medical profession. This risk of medical orthodoxy squashing innovation remains real. The fundamental purpose of the FDA premarket approval process is to separate the legitimate from the quackery based on actual evidence. Bypassing the approval process defeats this objective and those arguing in favor of eliminating the FDA's premarket role underestimate the risk to vulnerable populations.

## 2. The Variety of Existing Access Avenues

It is a misconception that FDA approval acts as an ironclad control point with very limited preapproval access. There are a variety of general and specific premarket access points in addition to the formal Phase II and III clinical trials. For example, there are premarket "clinical trial" systems such as the individual IND,<sup>47</sup> emergency use access,<sup>48</sup> and the expanded access provisions that provide access to drugs during the later stages of the clinical testing process.<sup>49</sup> There are "orphan drug" provisions with relaxed premarket approval requirements,<sup>50</sup> and the humanitarian device exemption provisions on the medical device front.<sup>51</sup> In addition, access restrictions are relevant only when the drug is not approved for any purpose. Otherwise, physicians and patients are free to use the product "off-label" for any purpose. Off-label use is widely practiced and provides substantial access to drugs for unapproved indications.

Certain diseases and patient populations may also have specific statutory provisions permitting earlier or faster access. The "fast track" provision for drugs used for life-threatening conditions is one example.<sup>52</sup> There are specific accelerated access provisions for HIV-related diseases<sup>53</sup> and financial in-

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47. 21 U.S.C. § 360bbb(b) (2006).

48. 21 U.S.C. § 360bbb-3(b) (2006 & Supp. 2009) (requiring a declaration of a national emergency).

49. *Id.* § 360bbb(c).

50. *Id.* §§ 360aa-360ee.

51. *Id.* § 360j(m).

52. 21 U.S.C. § 356 (2006).

53. *Id.* § 300cc-12 to -14.

centives and faster approvals for pediatric populations.<sup>54</sup> Clinicaltrials.gov provides patients with information on clinical trials of unapproved products in order to improve access.

In addition, medical tourism developed, in part, to provide access to therapies one cannot obtain in the United States. One of the earliest public examples of medical tourism was when Steve McQueen went to Mexico for eventually unsuccessful cancer therapy.<sup>55</sup> This trend has continued as evidenced by Farrah Fawcett's trips to Germany for cancer therapy not available in the United States.<sup>56</sup> Cost is, of course, another potential reason for medical tourism.

Thus, the drug approval decision point is not some binary system with access only postapproval. Many patients (with physician oversight and some level of regulatory protection) today do have access to unapproved products. Opening access as proposed by Epstein would actually have an impact on many fewer patients than may be commonly assumed. The risks of his proposal are, unfortunately, not similarly reduced. On the macro level, Epstein's concept has limited benefit and causes significantly greater harm. In FDA terms, it has a negative risk/benefit ratio.

### 3. Unequal Access to Information

Epstein begins to argue that the individual patient has the ability to collect and understand information about various treatments and therefore should have the right to make those decisions.<sup>57</sup> While perhaps romantic, Epstein immediately recognizes that the typical patient does not have the training or expertise to understand toxicology, pharmacology, pharmacogenetics, oncology, and so on.<sup>58</sup> Given this reality, Epstein does not finally advocate a pure libertarian approach. Rather, while substantially gutting the power and responsibility of the FDA, Epstein substitutes the physician and/or professional organiza-

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54. 21 U.S.C. §§ 355a, 355c (2006 & Supp. 2009).

55. Barron H. Lerner, *McQueen's Legacy of Laetrile*, N.Y. TIMES, Nov. 15, 2005, at F5. Note that Mr. McQueen was relying on the advice of a dentist for his decision to go to Mexico for an "unconventional" treatment. *Id.*

56. Miranda Hitti, *Farrah Fawcett's German Cancer Care*, WEBMD HEALTH NEWS, May 15, 2009, <http://www.webmd.com/cancer/news/20090515/farrah-fawcetts-german-cancer-care>. Cost is the other driving factor behind medical tourism.

57. Epstein, *supra* note 1, at 3.

58. *See id.* at 3.

tions as the key access control system.<sup>59</sup> He accepts some mandatory preaccess FDA testing and the validity of the prescription drug system—controlled by the physician—as a limit on patient autonomy. In essence, he accepts the need for a control mechanism between the patient and access to a therapeutic drug.

This substitution of physicians and professional organizations for the role of the FDA<sup>60</sup> is the linchpin of Epstein's argument. As he states, "The key conclusion is that voluntary current mechanisms . . . are far more likely to work across the board [than the FDA]."<sup>61</sup> This would depend upon the voluntary group doing at least as well or even better than the FDA in assembling and analyzing data on product efficacy, uses, and ultimate product value. Epstein clearly believes that the FDA is "second-best" at this task.<sup>62</sup> If this assumption is inaccurate, as seems to be the case, then Epstein's approach fails by its own terms.

When examined in detail, Epstein's argument depends upon the reality that the physician has greater knowledge of the specific patient, and the erroneous assumption that the physician and professional organization has equal or greater access to information and expertise than the FDA, and greater ability to effectively analyze such information. Epstein's argument also assumes that the physician has no conflicts of interest. As further detailed below in Part IV.B., it is impossible for any physician (or professional organization) to have greater access to information than the FDA, which has access to more information from a wider variety of sources than any professional organization and thus is better positioned to make general risk/benefit assessments.

#### 4. The FDA Process Provides More Transparency and Advances Public Input

Individual physician decisions occur in a more private, less transparent, and less accountable fashion than FDA decisions. Whether one likes them or not, FDA decisions are public and

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59. Even today, the physician functions as a gatekeeper. Essentially, all oncology drugs are prescription drugs and thus require physician approval for use even if the patient otherwise wants the drug. See 21 U.S.C. § 353(b) (2006).

60. Epstein, *supra* note 1, at 41.

61. *Id.*

62. *See id.*

are subject to some level of recourse through the democratic political process. The “fast track” provisions of 21 U.S.C. § 356 are, after all, mostly a response to political advocacy and pressure. Removing the FDA from the equation and transferring its role to physicians and organizations reduces the level of democratic oversight and accountability. Can patients force a medical association to change a practice guideline or policy? They cannot. Can patients petition the FDA or Congress for change? They can.<sup>63</sup>

The physician often has financial, professional, or other interests that are not aligned with the patient’s interests. The decision to use chemotherapy rather than radiation has a financial impact as different medical specialties are responsible for the different therapeutic approaches.

Responsibility for policy decisions regarding access to new drugs should be vested in the system or structure with the greatest transparency, public input, and accountability—and that is the FDA.

##### 5. The Public Is Affected by Individual Access Decisions

Epstein’s libertarian approach is based on the premise that the patient’s decision essentially affects only the patient. As such, the government should have little interest in such decisions. Yet that is not reality. First, therapeutic decisions by a patient often do affect the broader public, as the public is often involved in paying for therapies. In addition, if a therapy fails to cure a disease or causes some adverse event, the public pays the cost of ongoing care.

Second, some of those advocating government controls over access to experimental drugs argue that allowing patients access to an experimental drug reduces the ability to get subjects to participate in formal clinical trials. The argument runs: why join a clinical trial and have a fifty percent chance of getting the drug you want when you have a one-hundred percent chance of having the drug you want by simply getting your doctor to prescribe it? By allowing freer access, it will take more time and money before the FDA can approve (or certify under Epstein’s construct) the new drug.

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63. See, e.g., 42 U.S.C. § 1395x(t) (2006) (mandating the reimbursement of certain drugs used for cancer patients even if that particular use of the drug is not approved by the FDA); 42 U.S.C. § 300cc-12 (2006) (mandating expanded access to HIV drugs).

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Given that the public is directly and indirectly affected by access decisions, the public should have some level of involvement in generalized access decisions (in contrast to patient-specific medical decisions). The current system provides for public input in balance with patient autonomy.

#### 6. The Phase I Myth

Epstein, like the Abigail Alliance, argues that it is acceptable for the FDA to act as a safety gatekeeper through the Phase I clinical trial step.<sup>64</sup> The argument runs that the FDA does play a legitimate role in determining safety during Phase I clinical trials, and the public should have access to products that have successfully completed Phase I testing. This argument ignores the real meaning of Phase I clinical trials and misunderstands the concept of "safety" in real-life drug approvals.

First, Phase I clinical studies do not establish that a product is safe. Rather, they are an initial step to determine whether there is enough safety data to proceed. Phase I studies are incapable of making a final or conclusive safety determination because of (1) the small size of the studies (generally less than 100 subjects), (2) the nature of the subject (healthy volunteers), and (3) low dosing. Other than the most frank safety problem, a study of 80–100 subjects does not have the statistical power to identify real-life safety issues.

Also remember that, in real life, "safety" is a function of the disease and the benefit. Every drug has a side effect. Whether a drug is safe enough to use in a particular situation depends upon the nature of the disease, the benefit of the product, available options, and so on. None of this information is generated during the typical Phase I study.

Logically, if the FDA is to have a role in keeping unsafe products off the market, is there any reason why it should not play a similar role in keeping ineffective products off the market? The only possible answer is that unsafe products pose the risk of hurting people, while ineffective products do not pose the same risk. However, all drugs have risks for individual patients. Moreover, using an ineffective product often deprives the patient of the value of a more efficacious product.

Even Epstein balks at taking personal autonomy to the logical end of eliminating the FDA's gatekeeping role for safety. The question is then not whether the FDA should have a role in

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64. Epstein, *supra* note 1, at 20.

drug approval, but rather the nature of the role. There is no valid policy reason to permit FDA oversight of “safety” and then go the other direction regarding “efficacy” decisions. The two concepts are inexorably intertwined. Past efforts in the 1938–1962 timeframe to make this artificial distinction failed.

### C. THE OFF-LABEL CONUNDRUM

The reality of off-label use presents additional conceptual challenges. In all probability, each of us has used off-label products.<sup>65</sup> Some estimate that seventy percent of all pediatric prescriptions are off-label. Perhaps twenty percent of all prescriptions are off-label.<sup>66</sup>

If one argues that the FDA approval process must be in place to protect patients from unapproved products, why, then, is off-label use perfectly legal? The FDA does not regulate the practice of medicine and by statute physicians are free to use an approved product for any unapproved use.<sup>67</sup> The availability of off-label use thus undercuts much of the need for Epstein’s proposal. The FDA acts as a true gatekeeper only for the first approval of the drug in question for any purpose. After that point, the FDA acts much more as the certifying entity envisioned by Epstein.

Importantly, risks are reduced in off-label use following an initial approval for an unrelated use. First, basic toxicology and safety data has been developed during the approval of the first use. While different indications can present different toxicity and safety issues, there is a substantial body of basic scientific and clinical information available. Second, physicians often have more information about the drug for the off-label use given its other, on-label uses. Dosing information, metabolic data, drug interactions, basic pharmacology, mutagenicity information, and so on may be applicable across drug uses. Finally, the FDA has determined, in at least some cases, that the product has a positive risk/benefit ratio. So we have some level of confidence that the product is not total quackery.

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65. In this context, off-label simply means being used for a purpose other than as indicated on the FDA approved labeling. Remember that the FDA approves specific uses of drugs and not the drug itself.

66. See Ralph F. Hall & Robert J. Berlin, *When You Have a Hammer Everything Looks Like a Nail: Misapplication of the False Claims Act to Off-Label Promotion*, 61 FOOD & DRUG L.J. 653, 657–59 (2006) (describing some of the legal aspects of off-label uses).

67. 21 U.S.C. § 396 (2006).

So how can we deal with this paradox? We can go down Epstein's road and open up all uses after basic safety data is collected. (However, remember that safety is usually not an abstract question, but is intertwined with efficacy, dosage, and so on.) One could, as Epstein suggests, move the FDA from a regulatory gatekeeper to an information source or certifying entity.

Another option is to make any use of a product for an off-label purpose illegal. Such an approach certainly impinges patient autonomy and the perceived physician role. Such philosophical purity would probably flounder on the rocks of medical need and patient/physician desires. States generally regulate the practice of medicine and also could, on a state-by-state basis, prohibit some or all off-label uses. For example, Ohio has banned the use of Plan B products for off-label uses and that ban was upheld by the Ohio Supreme Court.<sup>68</sup> Such bans are exceedingly rare and in this case involve a highly politicized drug.

There are no totally satisfying answers to the conundrum posed by off-label use. The current approach to off-label use strikes a policy balance that is not philosophically pure but reflects the difficulty of these issues and the need for some practical balance.

#### D. SO WHERE DOES THAT LEAVE THE POLICY DEBATE?

As must be clear, there is no one "right answer" to where the line should be drawn between patient autonomy and the protection of overall public health and the prevention of fraud. As shown above, Congress and other policymakers continue the long struggle to define the balance. Epstein recognizes this reality and calls this issue "[o]ne of the thorniest questions in legal analysis."<sup>69</sup>

In many senses, this issue is a so-called wicked problem. "A 'wicked' problem has innumerable causes, is tough to describe, and doesn't have a right answer . . ." <sup>70</sup> They "occur in a social context; the greater the disagreement among stakeholders, the more wicked the problem. In fact, it's the social complexity of

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68. *Cordray v. Planned Parenthood*, 911 N.E.2d 871, 879 (2009).

69. Epstein, *supra* note 1, at 1.

70. John C. Camillus, *Strategy as a Wicked Problem*, 86 HARV. BUS. REV. 98, 100 (May 2008). The concept of "wicked" problems can be traced to the work of Rittel and Webber in the 1970s while at the University of California, Berkeley. See generally Horst W.J. Rittel & Melvin M. Webber, *Dilemmas in a General Theory of Planning*, 4 POL'Y SCI. 155 (1973).

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wicked problems as much as their technical difficulties that make them tough to manage.”<sup>71</sup>

We can and should continue the debate in order to properly strike the balance between patient autonomy and patient protection even if the odds of agreement or consensus are minimal. Often, one’s view depends on one’s perspective. If I am the cancer patient, I know the answer. Likewise, if I am seeing the aftermath of some medical quackery foisted off on a vulnerable relative, I know a (different) answer. The balance between patient autonomy and protection is subjective and ever-changing.

The competing policy issues inherent in this debate render extreme answers on either side of the conundrum questionable. There is a need for a centralist position that seeks to balance the differing needs. Taking an extreme or “purist” position as Epstein does undervalues the countervailing policy concerns and needs.

The fact that the issues are so complex makes more important the actual history and impact of various proposals. Rather than debating the esoteric aspects of this issue, we can and should look to real events. History illustrates the actual impact—good or bad—of various policy options and thus allows for a more accurate, data rich discussion of possible answers to this “wicked problem.”

### III. THE PAST AS PROLOGUE

Rather than getting trapped in a philosophical debate, I instead turn to the practical and the lessons of history. We can assess rather accurately via history whether Epstein’s proposal would work and its likely impact on public health by examining past regulatory schemas and practices. We can and should ask whether the system worked when professional organizations have played the key gatekeeping role in lieu of a strong pre-market approval system for drugs. History answers this question with a strong “no.” There have been major issues when professional medical organizations, personal physicians, and individual patients have unfettered access to any drug they want or see on TV.

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71. Camillus, *supra* note 70, at 100.

## A. 1938–1962 AND THE DESI PROCESS

One of the best tests of Epstein's proposed approach occurred during the 1938–1962 time frame.<sup>72</sup> In 1938, Congress replaced the 1906 Pure Food and Drug Act with the first version of the current Food Drug and Cosmetic Act. The 1906 Act had no premarket review or approval process for drugs. There was no prescription drug system requiring physician intervention. The premarket review system was created in 1938 following the sulfanilamide tragedy.<sup>73</sup> Congress and the public concluded that some level of government oversight was needed prior to a new drug hitting the market.

At this time, the FDA reviewed drug safety but didn't assess product efficacy,<sup>74</sup> which was left to the medical community (much as Epstein advocates). Physicians and medical societies had free rein to decide what products worked and when to use them. The role of the physician and voluntary medical society as the primary gatekeepers was further enhanced in 1950 when Congress formalized the prescription drug system. Patients had no stand-alone access to any drug, thus limiting patient autonomy.

This structure lasted until 1962 when, as a result of the thalidomide tragedy<sup>75</sup> and other public pressures, Congress required products to be efficacious as well as safe before marketing. Congress also required drugs approved from 1938–1962 to be reassessed for efficacy.<sup>76</sup> This established that the medical community (and manufacturers) had been using and marketing a substantial number of products without any meaningful data

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72. Prior to the 1920s, almost all drugs were natural products or extracts of naturally occurring plants or other material. As such, other than to remind everyone of the scope and number of quack remedies and snake oil salesmen, the differences in the state of pharmaceutical science renders the pre-1906 period of minimal practical value.

73. See *supra* notes 25–28 and accompanying text.

74. Regulation of the medical device world lagged behind the drug world. The major device regulatory system did not come into existence until 1976. The later timeframe for medical devices is probably due to both the variability in risk of medical devices and major technology advances in the 1960s and early 1970s coupled with several very public device issues—primarily the Dalkon Shield and Shiley Heart Valve. Given this timing difference, I will focus on the drug regulatory system.

75. See *supra* note 29 and accompanying text.

76. The provisions of the Kefauver-Harris Drug Amendments or the Drug Amendments of 1962 are now codified in 21 U.S.C. § 355 and implementing regulations. When the 1938 Act passed, Congress grandfathered in "old drugs" (see the definition of "new drug" in 21 U.S.C. § 321(p) (2006)). In contrast, in 1962 Congress required the 1938–1962 drugs to meet the new 1962 standards.

that the products worked; in many cases they in fact did not work. Without a federal regulatory oversight schema, the medical profession, including voluntary professional societies, had not separated the wheat from the chaff. There are a number of possible reasons for this failing: lack of data, lack of data access, or data being ignored. Whatever the reason, in 1962 Congress decided that the FDA had to step in and assume the gatekeeper role for assessing product efficacy.

The details of this reinforce the medical community's failure to fulfill its role as efficacy determiners. To accomplish the statutory task of determining efficacy for 1938–1962 drugs, the FDA commissioned the DESI study (Drug Efficacy Study Implementation), also referred to as the NAS/NRC (National Academy of Science/National Research Council) study. This major effort analyzed approximately 16,500 efficacy claims for about 4,000 products.<sup>77</sup> The results undercut the belief that physicians or the medical community in general can either determine drug efficacy or adopt practice approaches that reject inefficacious drugs.

In its key report,<sup>78</sup> the DESI study used five categories for efficacy claims made regarding specific drug products.<sup>79</sup> As can be seen in the following table, the number of products with strong and positive efficacy data supporting their use was shockingly small.

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77. The Drug Efficacy Study of the National Research Council's Division of Medical Sciences, 1966–1969, [http://www7.nationalacademies.org/archives/druefficacy.html#P177\\_8632](http://www7.nationalacademies.org/archives/druefficacy.html#P177_8632) (last visited May 11, 2010); see also Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 GEO. L.J. 185, 207–12 (1971).

78. While the main report was issued in 1969, a number of drugs remained unanalyzed for many years. The 1969 study assessed, in general, the most important products.

79. The categories and their short definitions are as follows:

Effective—Self-explanatory and evidence-based.

Probably effective—Additional evidence required to determine efficacy.

Possibly effective—Little evidence of effectiveness, but possibility of additional evidence should not be ruled out.

Ineffective—No acceptable evidence to support claim.

Effective, but—Effective for claimed indication (use) but not approved form of treatment because better, safer, or more conveniently administered drugs are available.

Rating	Number of Claims	% of Claims
Ineffective	2442	14.7
Possibly Effective	5778	34.9
Probably Effective	1204	7.3
Effective	3159	19.1
Effective, but	3990	24.0
Total	16,573	100

Essentially, fifty percent of indications for use had little or no evidence to support the efficacy of the claimed use. Despite this glaring gap in evidence or actual negative scientific data, physicians were using these products routinely. In this almost quarter-century experiment, the medical community did not, of its own accord, develop and utilize robust efficacy data. Why should we think today that the medical community would act differently?

The DESI study forces one to seriously question the ability or will of the medical profession—absent regulatory oversight—to assess product efficacy or to generally conform medical practice to best practices. If we return to the pre-1962 system as Epstein suggests, can we expect a different outcome today?

#### B. COMPARATIVE EFFECTIVENESS ISSUES CONFIRM THE PROBLEM WITH RELYING ON VOLUNTARY ASSOCIATIONS

One can of course argue that the problems found through the DESI study were a long time ago, that the medical community has changed, or that we have new capabilities that render history uninformative—Santayana's famous warning to the contrary.<sup>80</sup> After all, today we have more doctors, more specialization, more research, globalization, and a quantum leap in information technology. All of this could lead one to conclude that today's doctors and today's medical professional organizations are substantively different from their predecessors and have developed strong efficacy data to support their treatment decisions. To reach this conclusion, however, one would also have to conclude that the increased time and financial pressures facing physicians and the explosion in medical complexity and information sources have not negatively impacted the ability or willingness of the medical community to conduct these assess-

80. GEORGE SANTAYANA, *THE LIFE OF REASON: OR THE PHASES OF HUMAN PROGRESS* 82 (1953) ("Those who cannot remember the past are condemned to repeat it.").

ments. Unfortunately, the reality is that physicians often lack the information that Epstein requires of them. The current focus on comparative effectiveness demonstrates that the medical profession individually and collectively has not met the obligation that Epstein's proposal requires and demands. The expert consensus from many perspectives is that in too many cases we don't have adequate data on which drug or therapy is better for a specific disease.<sup>81</sup> Shouldn't physicians know which drugs or therapies work best and then use those superior therapies? While logic clearly says "yes," the reality is that this is not a routine occurrence in today's medical environment.

A problematic foundation of Epstein's approach is thus that the medical community and professional societies can do a better job than the FDA in assessing all available evidence about a particular therapy and making efficacy determinations. Comparative effectiveness is the fancy term for looking at two or more therapies for a specific disease or condition and deciding which is best, which is what Epstein envisions the medical community itself providing. But current data on the extent of the gaps in comparative effectiveness data and in the use of existing data argues that any such transfer of responsibility may be fraught with peril.

The FDA, further, has not felt that it is authorized by statute to use comparative effectiveness in approval decisions. The approval standards in 21 U.S.C. § 355(c) and (d) require the FDA to review the drug on the basis of the intended labeling and use of the product. In testimony leading up to the 1962 amendments, an agency representative stated, "[w]e do not seek the authority [and] . . . we would not and do not want to

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81. There are numerous such conclusions. *See, e.g.*, CONG. BUDGET OFFICE, RESEARCH ON THE COMPARATIVE EFFECTIVENESS OF MEDICAL TREATMENTS: ISSUES AND OPTIONS FOR AN EXPANDED FEDERAL ROLE (2007), available at <http://www.cbo.gov/ftpdocs/88xx/doc8891/12-18-ComparativeEffectiveness.pdf>; *Initial National Priorities for Comparative Effectiveness Research*, INST. OF MED., June 2009, available at <http://www.iom.edu/Reports/2009/ComparativeEffectivenessResearchPriorities.aspx> [hereinafter *National Priorities*]; Michael Hochman & Danny McCormick, *Characteristics of Published Comparative Effectiveness Studies of Medications*, 303 J. AM. MED. ASS'N 951 (2010); Alvin I. Mushlin & Hassan Ghomrawi, *Health Care Reform and the Need for Comparative-Effectiveness Research*, 362 NEW ENG. J. MED. e6 (2010); Peter J. Neumann & Sean R. Tunis, *Medicare and Medical Technology—The Growing Demand for Relevant Outcomes*, 362 NEW ENG. J. MED. 377 (2010).

pass on relative efficacy."<sup>82</sup> The medical community, not the FDA, was essentially charged with determining which therapy or drug was better than another once the FDA had fulfilled its initial gatekeeping role of assuring that the drug was safe and efficacious for its labeled or intended purpose. Unfortunately, as discussed in more detail below, the medical community has not fulfilled this role in any way near the extent now desired.

This significant gap is confirmed by the major push in this country (and others) by policymakers, regulators, the medical profession, payors, and others for substantially enhanced comparative effectiveness research, data, and utilization. This effort starts with the conclusion that current medical practitioners too often do not know or utilize the best therapeutic approach. It postulates that the medical community has not, as Epstein would require, developed or adopted evidence-based approaches to health care decisions (even in situations absent FDA oversight).

No existing laws or regulations prohibit or restrict the medical profession from assessing product efficacy and safety or determining best practices and practice guidelines. If the medical community currently does not do so or goes so far as to use nonevidence based practice guidelines, then one should seriously question turning over the FDA's regulatory oversight to these groups.

The need for substantially enhanced comparative effectiveness data has been established by the medical community, Congress, the Congressional Budget Office, the Institute of Medicine, and payors, including the federal government and patients.<sup>83</sup> This commentary is not the place for an exhaustive discussion of the need for comparative effectiveness. However, a few examples prove that voluntary medical associations have failed to assemble, disseminate, or follow best practices when deciding which treatment to use for a specific disease.

In 2007, the Congressional Budget Office stated that "hard evidence is often unavailable about which treatments work best for which patients."<sup>84</sup> The CBO report goes on to outline signifi-

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82. *Hearings Before the Senate Subcomm. on Antitrust and Monopoly of the Comm. on the Judiciary*, 87th Cong. 2585, 2605 (1961) (statement of Secretary Ribicoff).

83. *See supra* note 81.

84. CONG. BUDGET OFFICE, RESEARCH ON THE COMPARATIVE EFFECTIVENESS OF MEDICAL TREATMENTS: ISSUES AND OPTIONS FOR AN EXPANDED FEDERAL ROLE 1 (2007), available at <http://www.cbo.gov/ftpdocs/88xx/doc8891/12-18-ComparativeEffectiveness.pdf>.

cant variations in treatments utilized in different geographic areas of the United States.<sup>85</sup> The best medical treatment for the same cancer doesn't differ between parts of the country. Regional variations are attributed to a lack of good data, payment pressures, historical practices, and the level of compliance with existing practice guidelines.

In its report, the CBO directly addressed the question of whether private, nongovernmental entities, including payors, will or should be expected to conduct comparative effectiveness research. After discussing some current but limited private comparative effectiveness, CBO went on to state: "Notwithstanding those current efforts, the private sector generally will not produce as much research on comparative effectiveness as society would value. The knowledge created by such studies is costly to produce—but once it is produced, it can be disseminated at essentially no additional cost . . ."<sup>86</sup> The CBO's conclusion that private efforts cannot fill the need for comparative effectiveness strikes directly at the heart of Epstein's argument. In order to continue down his road, one must conclude either that the CBO and others are wrong or that the voluntary medical organizations and other stakeholders will suddenly change their ways when presented with this new opportunity. Neither seems likely.

The CBO report is not alone. In early 2009, as part of the economic stimulus program, Congress allocated \$1.1 billion, spread among several government entities, for comparative effectiveness research.<sup>87</sup> Even Congress doesn't spend that amount of money unless there is some perceived need. As a part of this spending, the Institute of Medicine (IOM) conducted a detailed assessment of comparative effectiveness needs and priorities. IOM findings are, to be blunt, scary if one wants to rely on the medical establishment as proposed by Epstein. The IOM report states:

- Nationally "less than half of all treatments delivered today are supported by evidence."<sup>88</sup>

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85. *Id.* at 12–15.

86. *Id.* at 8.

87. Agency for Healthcare Research and Quality, U.S. Dep't of Health & Human Servs., AHRQ and the Recovery Act, <http://www.ahrq.gov/fund/cefarr.htm> (last visited Apr. 24, 2010).

88. *National Priorities*, *supra* note 81, at 30.

- Relatively few practice guidelines from the American College of Cardiology are based on "high-quality evidence."<sup>89</sup>
- "[T]wo-thirds of recommendations contained in 51 guidelines for treating lung cancer were not evidence-based."<sup>90</sup>
- Even when guidelines exist, they are often not followed. Patients in the United States may receive only 55% of the recommended care.<sup>91</sup>
- Only 46.5% of children and youth received the recommended care.<sup>92</sup>

The IOM has clearly found major gaps both in the identification and development of valid practice guidelines and in the actual use of practice guidelines by the physician community. Both of these factors must, however, be true for Epstein's construct to work.

The medical community itself recognizes the need for comparative effectiveness, as well as the fact that it has not done nearly enough to develop such data in the past and has not had enough effect on medical practices.<sup>93</sup>

History, starting with the DESI studies and continuing up to today's efforts to remedy the lack of robust comparative effectiveness data, casts serious doubt on the foundational assumption underlying Epstein's position that physicians and medical societies will develop and utilize drug efficacy data better than the FDA.

#### IV. THE VOLUNTARY ASSOCIATION CHALLENGE

Epstein asserts that professional associations are better equipped or more capable of generating robust efficacy data and acting on that data in making medical choices. While pa-

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89. *Id.*; see also Pierluigi Tricoci et al., *Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines*, 301 J. AM. MED. ASS'N 831 (2009).

90. *National Priorities*, *supra* note 81, at 30; see also Linda H. Harpole et al., *Assessment of the Scope and Quality of Clinical Practice Guidelines in Lung Cancer*, 123 CHEST (Supp.) 7S (2003).

91. *National Priorities*, *supra* note 81, at 32–33; see also Elizabeth A. McGlynn et al., *The Quality of Health Care Delivered to Adults in the United States*, 348 NEW ENG. J. MED. 2635 (2003).

92. *National Priorities*, *supra* note 81, at 33; see also Rita Mangione-Smith et al., *The Quality of Ambulatory Care Delivered to Children in the United States*, 357 NEW ENG. J. MED. 1515 (2007).

93. See *supra* note 81.

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tients are the ultimate decision makers, even Epstein recognizes that the average patient does not have the training, expertise, or background to dissect and understand complex medical information.<sup>94</sup> Unfortunately, history and a close examination of the structure and capacity of voluntary professional organizations undercut this assumption. The inescapable conclusion is that the FDA is in a substantially better position than any voluntary professional association to collect and analyze data from multiple sources.

Remember that both Epstein and I are concentrating on the structural or statutory issues surrounding agency and professional society power and authority. Whether the agency or any one professional society is actually effective in exercising these powers is a different question. Epstein is spot on with his view that structural issues or performance need to be addressed at the policy level by Congress. Performance issues should be addressed by management changes, resource increases, or operational changes. This latter set of issues is outside the scope of this debate.

#### A. VOLUNTARY PROFESSIONAL ASSOCIATIONS HAVE A POOR HISTORY OF GENERATING ROBUST OR PERHAPS EVEN VALID PRACTICE GUIDELINES

As discussed earlier, medical associations today are completely free to develop and implement practice guidelines. As has been established by the current need for comparative effectiveness data, medical associations have not fulfilled this need.

There are many reasons for this. Medical associations lack the structure and organization to do the research and analyze the results. Remember, these are voluntary organizations. As detailed below, they have incomplete access to information. In addition, medical associations are generally silos of specific specialties. There are, for example, a number of relevant but individual medical associations within the oncology field, each with its own area of specialized knowledge. There are surgical associations, chemotherapy-centric groups, and radiation specialty groups. Determining the best therapy may require assessing therapeutic options across all specialties. It is difficult, if not impossible, for the medical community consistently to have cross-cutting, cross-disciplinary groups that have the relevant expertise in all subspecialties. Individual professional

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94. Epstein, *supra* note 1, at 3–4.

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medical groups may also lack expertise in basic science areas such as pharmacokinetics, toxicology, and pharmacogenetics.

There is simply no way to compel a voluntary medical association to research or assess any new therapy or to create, reassess, or modify any practice guideline. Individual physicians likewise struggle to keep current with all medical developments and generally lack the time, resources, facilities or expertise to conduct statistically valid research. One can find exceptions, but asking voluntary medical associations to assume the gatekeeper function is asking them to do more than should be expected. They are not government agencies and should not be treated as such.

#### B. THE FDA HAS BETTER AND FASTER DATA ACCESS

Robust efficacy determinations or the development of valid practice guidelines require access to complete and current data. Logically, the entity with the best access to data is best positioned to make efficacy determinations. The FDA definitionally has superior data access compared to private medical associations. Several examples demonstrate this fact.

First, except for some individual medical records,<sup>95</sup> there is no data that a medical professional can access that the FDA cannot. That alone says that the FDA is at least on equal footing with medical associations and doctors. In actuality, the FDA has superior data access from a number of sources.

Companies (and to a much more limited extent, health care providers) are required to provide complete internal and external scientific information to the FDA as part of the application process and ongoing reporting obligations.<sup>96</sup> The FDA has the statutory authority to inspect companies and to inspect clinical trial sites and clinical data.<sup>97</sup> Clinical trial information on new products is submitted to the FDA and a subset of that informa-

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95. Even with regard to personal medical records, the government can access millions of records through the Medicare/Medicaid systems and through other military and nonmilitary employee health care systems. These data sets are generally more than ample for any data searches or retrospective case control studies.

96. See 21 C.F.R. § 314 (2009) and 21 C.F.R. § 814 (2009) for examples of regulatory obligations on companies to submit complete data sets (and to periodically update the data set) with both public (published) information and confidential information during both the approval process and as part of ongoing reporting requirements.

97. 21 U.S.C. §§ 360j(c), 374 (2006); 21 C.F.R. §§ 312.58, 312.68, 812.145.

tion is posted on a publicly accessible website.<sup>98</sup> A voluntary organization cannot require such submissions, have complete access to all of the information available to the FDA, inspect clinical trial sites, or conduct regulatory inspections.

Moreover, companies are required to promptly submit case reports (confirmed and unconfirmed) about deaths, serious injuries, or “near misses” involving their products.<sup>99</sup> No voluntary professional society can (1) require such submissions, (2) uncover missing data during inspections, or (3) obtain such information from multiple sources in a timely fashion. These reports can serve as important data or indicators of product issues. Further, only a government regulatory agency can impose testing obligations, postmarket programs such as Risk Evaluation and Mitigation Strategies (REMS), or product tracking systems.

The FDA can also access information from submissions or reports from multiple companies. Generally speaking, certain detailed data included in approval submissions of various types<sup>100</sup> are trade secrets and therefore confidential.<sup>101</sup> The FDA, however, has access to such information and is clearly authorized to use confidential data from one submission to assess the safety and efficacy of another product.<sup>102</sup> Private groups do not have such rights and would struggle to have prompt access to such confidential information. Unless the voluntary association is somehow deputized with governmental powers to demand data, compel compliance, conduct inspections, and guarantee confidentiality (a concept fraught with political, practical, and legal barriers), only the FDA will have complete data access.

Furthermore, the FDA also has access to information from other regulatory agencies, both U.S. and non-U.S. Various governmental agencies can and do exchange information with the

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98. See U.S. National Institutes of Health, ClinicalTrials.gov, <http://www.clinicaltrials.gov> (last visited Apr. 24, 2010).

99. See 21 C.F.R. § 314.80 for adverse drug reporting requirements (generally referred to as ADRs) and 21 C.F.R. § 803 for device adverse event reporting obligations (generally referred to as MDRs).

100. Examples of such submissions include New Drug Applications (NDAs), Investigational Drug Applications (INDs), Premarket Approvals (PMAs), Investigational Device Exemptions (IDEs) and Biological License Applications (BLAs).

101. 21 U.S.C. § 379; 21 C.F.R. §§ 314.430, 814.9.

102. 21 U.S.C. § 355(d) and (e) clearly contemplate that the FDA can use data from any source in making approval or withdrawal decisions.

FDA regarding scientific developments, new research, product information, medical issues, and so on via a number of mechanisms, including statutory requirements and interagency memoranda of understanding. Via these processes, the FDA can obtain data from the Center for Medicaid and Medicare Services (CMS), other parts of HHS such as the Office of the Inspector General, Agency for Health Research and Quality (AHRQ), the Department of Justice (and various U.S. Attorney offices), the FTC, and the SEC.<sup>103</sup> The FDA can also access information from individual states. Such data can be used prospectively to identify best practices, to obtain information from inspections or enforcement actions, or to identify efficacy or safety issues. A private, voluntary entity is greatly hampered in accessing such information.

On the international front, the FDA has established information exchanges with a significant number of foreign regulatory agencies.<sup>104</sup> This provides the FDA with access to even more data and the ability to work with these counterpart agencies to develop product usage information or recommendations and to identify safety and/or efficacy issues.

If one believes that robust data is a sine qua non to determining best practices, safety, efficacy, product risks, or any similar determination, then the responsibility for such determinations should primarily rest on the entity with the best access to the greatest quantity and quality of data. The FDA, not a voluntary professional organization, has this access. One is hard pressed to identify any significant data source that a private professional society could access that the FDA could not.<sup>105</sup> Data availability alone points towards the FDA, not some private group, having the key role in product approvals.

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103. See, e.g., 36 Fed. Reg. 18,503, 18,539 (Sept. 16, 1971).

104. See U.S. Food & Drug Admin., Memoranda of Understanding and Other Cooperative Arrangements, <http://www.fda.gov/InternationalPrograms/Agreements/MemorandaofUnderstanding/default.htm> (last visited May 11, 2010) (providing an exhaustive list of such arrangements across a wide variety of substantive areas).

105. Remember that the FDA has the ability to convene expert panels to provide input to the FDA on complex scientific and medical questions. This is commonly done for complex approval decisions or controversial product decisions. These advisory groups are regulated by the Federal Advisory Committee Act (FACA), 5 U.S.C. app. §§ 1–16 (2006). These requirements include transparency and conflict of interest provisions.

C. THE FDA HAS SUPERIOR RESOURCES AND ACCESS TO EXPERTISE

Collecting, analyzing, deciding, and monitoring efficacy information and practice guidelines are resource-intensive activities. Studies and data analysis simply cost a lot of money. For example, Congress has appropriated \$1.1 billion for comparative effectiveness studies, with more money needed.<sup>106</sup> Individual physicians and professional societies simply cannot match these resources—one simple study on just one use of one particular medical device will take three years and cost \$3.5 million. Unless we are comfortable with efficacy decisions and practice guidelines being developed from anecdote and guesstimates, substantial time and money is required.

The sources of such resources are few. The FDA can do it using general revenue funds and user fees, product sponsors can on occasion fund such research as part of the cost of an approval (and pass some or all of the cost on to consumers), payors can fund it (and pass some or all of the cost on to consumers), or voluntary associations can attempt to fund such research—with no viable funding mechanism or ability to pass the costs to consumers, industry, or the government. Professional societies have access to their members and perhaps ancillary support from other volunteers, professional societies, private foundations, and perhaps from home institutions. This support, however, is at best ad hoc.

In addition to financial resources, as discussed earlier, the FDA can leverage scientific and medical expertise from across the government and can reach out to nongovernment experts via the advisory panel process. The FDA has access to whatever information the medical community possesses through formal and informal means. Private medical associations can never hope to match the FDA's resources or access to information and expertise. This critical factor alone undercuts the ability of professional societies to fulfill this need and reinforces that the FDA is in a better position to fulfill this responsibility on an ongoing basis.

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106. Press Release, The National Academies, Institute of Medicine Report Recommends 100 Initial Priorities for Research to Determine Which Health Care Approaches Work Best (June 30, 2009), *available at* <http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=12468>.

#### D. VOLUNTARY PROFESSIONAL ORGANIZATIONS FACE CONFLICT OF INTEREST ISSUES

Voluntary professional organizations also face a number of conflict of interest issues. Physicians are compensated based on therapies utilized and interventions employed. A surgical procedure may result in a larger payment to the physician than simply prescribing a drug. Each subspecialty has a financial and professional incentive to boost utilization of its therapeutic approaches. Overutilization of specific therapies is something that constantly worries payors and is one of the driving factors behind the push for comparative effectiveness. Further, professional reputations and academic careers are made or broken on what therapy "wins." These career issues also serve as inescapable conflicts of interest.

Furthermore, remember that there is not one "anointed" professional society for a specific disease or therapy. For example, a large number of professional societies are active in the cancer world. These can be divided by specialty or by disease.<sup>107</sup> Conclusions and approaches may well vary between professional societies. The viewpoint of a surgical society may well favor surgical interventions while radiologists may well favor a different therapeutic approach. The conclusions of any one such professional association are subject to question given the potential biases involved. This also leads to the unaddressed issue of how to deal with conflicting or contradictory recommendations from different professional societies. And who decides which professional society is right when there is some disagreement? Epstein seemingly leaves this for individual physicians to sort out, which is probably an impossible task.

#### E. VOLUNTARY PROFESSIONAL ORGANIZATIONS LACK TRANSPARENCY, PROCEDURAL RIGHTS, AND ACCOUNTABILITY

The FDA processes have a significant level of transparency<sup>108</sup> and are subject to the democratic processes. FDA decisions

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107. See, e.g., Laurie Barclay, *New Breast Cancer Screening Guidelines Opposed by Societies*, MEDSCAPE MEDICAL NEWS, Nov. 19, 2009, <http://www.medscape.com/viewarticle/712720> (documenting recent controversy between several professional societies over mammograms and breast cancer).

108. While there are often complaints about a lack of transparency at the FDA (and many of these complaints are justified), the FDA has publicly announced initiatives to improve transparency, including the creation of a transparency task force. U.S. Food & Drug Admin., FDA Transparency Task Force, <http://www.fda.gov/AboutFDA/WhatWeDo/FDATransparencyTaskForce/default.htm> (last visited Apr. 24, 2010). Congress also has enacted transparency re-

are often made after public meetings. New regulatory policies must go through the notice and comment administrative law processes. Lesser matters may go through good guidance practices which include public notice and the opportunity to comment.<sup>109</sup> Any aggrieved party can petition the FDA to adopt or change its policies through administrative law provisions.<sup>110</sup> The FDA publishes various notices regarding product approvals, labeling changes, recalls, and product withdrawals. In short, the FDA has transparency and procedural rights and remedies which simply do not and cannot exist within a private medical association.

Likewise, the FDA can be held accountable by elected officials. Government oversight hearings are a part of life for the FDA. Different administrations have different policy priorities and policy views. The Commissioner of the FDA must be approved by the Senate. The press routinely praises or, more commonly, criticizes FDA actions. There are obvious differences between FDA policies under the Obama administration and policies under the Bush administration. Voluntary medical associations answer only to their members. If we assign the gatekeeper role to voluntary medical associations, the lack of any meaningful accountability, transparency, or oversight renders such a system less responsible to popular will than is true under the FDA.

This accountability and transparency is particularly critical when one realizes that, in the end, the decision to approve a new drug or device is based on public policy, balancing risk and benefit. This is not a pure scientific decision; rather, science is one key input into the risk/benefit decision. The debate over access to HIV/AIDS drugs is just one example of product approvals being a public policy balancing act.<sup>111</sup> Transferring public policy decisions to private entities violates democratic principles.

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lated statutes (such as the Freedom of Information Act and the Federal Advisory Committee Act (FACA)) to mandate transparency. Congress also exercises an oversight role to ensure adequate transparency. No such mechanisms exist for private medical associations.

109. 21 C.F.R. § 10.115 (2009).

110. *Id.* § 10.30.

111. The passage of accelerated access and approval provisions for life threatening diseases such as AIDS as set forth in provisions such as 21 U.S.C. § 356 (2006) and 21 U.S.C. § 360bbb (2006) are examples of public pressure changing access rules.

F. THE EXISTENCE OF FDA LABELING GENERALLY DOESN'T  
PRECLUDE DIFFERENT PRACTICE GUIDELINES OR  
RECOMMENDATIONS

Having said all of this, whatever role or benefit voluntary medical associations can and should play in defining practice guidelines and advising on therapeutic options, it already exists today. Whatever value they might offer is already within reach. These entities should be continually encouraged to play a significant role in assessing product performance, working towards product approvals, providing expert input to the FDA, developing practice guidelines, analyzing data, conducting research, and advancing medical care in general. However, this does not mean that these groups are in a position to supplant the FDA. Furthermore, has anyone asked whether these associations want this responsibility?

CONCLUSION

The crux of Epstein's argument is that the current FDA oversight system deprives patients (and their physicians) of complete control over therapeutic decisions because the FDA must approve a medical product for some use before it is available to the public. Thus, he argues, the FDA is impinging on personal freedom and maximal medical choice. To remedy this, he proposes to eliminate "permittis" by reducing the FDA to an advisory/information role (post-Phase I safety determinations) and by elevating private medical groups to serve as the key gatekeeper responsible for identifying safe and effective therapies.

Has Epstein raised a critical issue? The answer is clearly "yes." Has Epstein found the answer? I think not. I differ from him on policy grounds because his construct almost completely devalues two of the key missions of the FDA: enhancing patient outcomes and protecting the patient/consumer. Even if one is inclined to agree with Epstein's philosophical views, history and logic demonstrate that his solution simply doesn't work in real life and has been repeatedly rejected by the body politic. Individual patients, physicians, or volunteer medical associations simply cannot be expected to have the expertise, resources, time, or inclination to collect and analyze all of the data on each specific therapy and otherwise to do the FDA's job.<sup>112</sup>

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112. There are obvious constitutional questions with assigning actual government authority to a nongovernmental entity. *See, e.g.,* United States v. An

The current regulatory system is not perfect. Reforms and ongoing improvements are clearly needed. But the answer is to constantly work to fix and optimize the system, not to eliminate it. As history shows, turning the FDA into merely an advisory or informational entity will harm patients.

In the end, Epstein raises a question that has vexed policy makers for decades. I appreciate the issue but the answer is not to turn back the clock seventy-five years. Epstein has raised the right question, but delivered the wrong answer.

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Article of Drug Ova II, 414 F. Supp. 660 (D. N.J. 1975) (discussing “drugs” in interstate commerce). As such, Epstein correctly argues for a voluntary role for medical associations and physicians rather than a legal, authoritative role. In such a situation, there is, at most, limited recourse if such a voluntary group either does not fulfill this task or fulfills it negligently. Likewise, there is little or no accountability, transparency, or structured process for public input into the decisions of voluntary organizations.