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Article

Against Permittitis: Why Voluntary Organizations Should Regulate the Use of Cancer Drugs

Richard A. Epstein[†]

INTRODUCTION

One of the thorniest questions in legal analysis concerns the longstanding tension between individual autonomy and social control. The principle of autonomy, or individual self-rule, holds a strong grip on everyone's imagination by posing the following question: If I am not allowed to control my own destiny, just who can? In this context, autonomy functions as the first and most powerful line of defense against the domination of one person by another and of all individuals by the state. At the same time, the faithful adherence to the principle of individual autonomy could be almost too strong, because it precludes the ability of the state to organize the provision of public goods. Writing in 1965, Mancur Olson, Jr. showed how the absence of state intervention could lead to the underprovision of key public goods such as national defense.¹ Three years later, Garrett Hardin showed how the failure to impose social controls could lead to the tragedy of the commons, whereby excessive hunting

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1. MANCUR OLSON, JR., *THE LOGIC OF COLLECTIVE ACTION* 14 (1965).

or fishing would eventually bring about the premature collapse of wildlife populations.²

Just as the case for state regulation has become a more powerful tool for dealing with public goods and common-pool problems, the principle of autonomy continues to hold sway with respect to the decisions that individuals make over their own bodies. This issue is of supreme importance in dealing with medical matters, where the autonomy principle offers guidance on the ancient question of whether to accept or reject medical treatments. That principle received perhaps its most famous short formulation by Judge Benjamin Cardozo who wrote nearly a century ago:

Every human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient's consent commits an assault, for which he is liable in damages. . . . This is true, except in cases of emergency where the patient is unconscious, and where it is necessary to operate before consent can be obtained.³

Notwithstanding the pervasive concerns of collective action, there is little doubt that *half* of this thesis still holds true today. The *defensive* use of personal autonomy allows individuals to refuse medical treatment that others may have concluded, even rightly, would work for their own benefit.⁴ At the same time, the *offensive* use of autonomy—namely the right to accept treatment with consent—has been widely rejected today, especially in connection with the use of drugs. No individual today can demand whatever medical treatment he or she wishes to receive. The modern position has been put forcefully by George Annas: “Patients in the United States have always had a right to refuse any medical treatment, but we have never had a right to demand mistreatment, inappropriate treatment, or even investigational or experimental interventions.”⁵ Evidently, the road to unrestricted medical usage is blocked by daunting institutional obstacles, where most notably the Food and Drug

2. Garrett Hardin, *The Tragedy of the Commons*, 162 SCI. 1243, 1244, 1248 (1968); see also H. Scott Gordon, *The Economic Theory of a Common Property Resource: The Fishery*, 62 J. POL. ECON. 124, 125–26 (1954).

3. *Schloendorff v. Soc’y of N.Y. Hosp.*, 105 N.E. 92, 93 (N.Y. 1914), *abrogated on other grounds* by *Bing v. Thunig*, 143 N.E.2d 3, 9 (N.Y. 1957), *superseded by statute*, N.Y. PUB. HEALTH LAW § 2805-d (McKinney 2007), *as recognized* in *Retkwa v. Orentreich*, 584 N.Y.S.2d 710 (N.Y. Sup. Ct. 1992).

4. See Richard A. Epstein, *The Erosion of Individual Autonomy in Medical Decisionmaking: Of the FDA and IRBs*, 96 GEO. L.J. 559, 566–80 (2008).

5. George J. Annas, *Cancer and the Constitution—Choice at Life’s End*, 357 NEW ENG. J. MED. 408, 410 (2007).

Administration (FDA) must license a drug before it may be made available for general sale or use.

The common justifications for imposing this restriction rest on the assumption that ordinary individuals cannot collect or correctly interpret the information that is needed to make intelligent decisions on these matters. Therefore, the argument continues, state intervention is necessary to guard against the exploitation of incompetent patients by unscrupulous purveyors of medical care. Indeed, a close reading of the well-known 1979 Belmont Report shows how easy it is to convert an implicit endorsement of the autonomy principle into a strong call for increased government oversight of medical treatment.⁶

This current uneven acceptance of the autonomy principle manifests itself most clearly in the area of drug regulation. The FDA can currently keep drugs off the market if it so chooses, thereby limiting the scope of autonomous choices. Once a drug makes it to the marketplace, however, the normal principles of individual autonomy apply. Within this context it is critical to recall that ordinary individuals do *not* make their decisions in an isolated position, akin to Robinson Crusoe stranded on a desert island.⁷ Rather, they consciously rely on voluntarily chosen experts to assist and guide them in their choices. In effect, the desirability of autonomous choices rests on the belief that competent individuals, supported by advice from families, friends, and professionals, can, on average, make better decisions about their own health care than any government agency that seeks to protect them from their own mistakes.

The central challenge in modern drug regulation is to explain why the FDA should be maintained as a public gatekeeper, instead of being relegated to the more modest role

6. See NAT'L COMM'N FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH 4–5 (1978); see also Larry R. Churchill, *Toward a More Robust Autonomy: Revising the Belmont Report*, in BELMONT REVISITED 111, 111 (James F. Childress et al. eds., 2005) (criticizing the Belmont Report's "weak and distorted understanding of self-determination"); Richard A. Epstein, *Defanging IRBs: Replacing Coercion with Information*, 101 NW. U. L. REV. 735, 741–45 (2007) (discussing the Belmont Report's conceptual errors). For a more critical view on the licensing of research performed on human subjects, see Philip Hamburger, *Getting Permission*, 101 NW. U. L. REV. 405, 406–10 (2007).

7. See DANIEL DEFOE, ROBINSON CRUSOE 234, 302 (Thomas Keymer ed., Oxford 2007) (1719). The original Robinson Crusoe was said to have spent twenty-seven years in isolation on a tropical island located somewhere in the Caribbean.

in which it merely *certifies* various products as “safe and effective.” In the latter role, the FDA would not have a monopoly position but would rather act as one of many certification agencies that offer advice on what drugs to use and what drugs to avoid. Indeed, it is just this position that I wish to defend. My thesis is that we should remove, or at least sharply curtail, FDA control of the licensing of new drugs. This thesis will sound harsh to individuals who instinctively accept the proposition that the government’s police power gives it the unquestioned right to regulate for the health and safety of the population.⁸

To demonstrate this thesis, my analysis concentrates largely on that part of the medical thicket where the case for FDA oversight is normally thought to be at its zenith: the use of cancer drugs which are fraught with evident side effects, many of which can prove fatal. In dealing with this issue, I freely admit that I have no expertise on any matters that deal with the relative merits of the various therapies that are, or may be, used to attack cancer. Those tasks should be left to patients in conjunction with their own doctors, often on the strength of knowledge acquired from nongovernment sources. I do, however, think that a lawyer has something to contribute to understanding the institutional arrangements that are likely to lead to responsible individual decisions. In making this case, I start from the classical liberal presumption that government intervention must be regarded as a bad until it is shown to be a good.⁹

That presumption rests on two grounds, both fully applicable to the FDA. First, intervention requires administrative expenditures by the state and imposes compliance costs on the parties. The imposition of these social costs can be justified only

8. Indeed, the Supreme Court has recognized the government’s sweeping power to protect the population’s health:

Nothing in the history of the 1938 Food, Drug, and Cosmetic Act, which first established procedures for review of drug safety, or of the 1962 Amendments, which added the current safety and effectiveness standards in § 201(p)(1), suggests that Congress intended protection only for persons suffering from curable diseases. . . . Both Reports note with approval the FDA’s policy of considering effectiveness when passing on the safety of drugs prescribed for “life-threatening disease.”

United States v. Rutherford, 442 U.S. 544, 552–53 (1979) (footnotes omitted).

9. See, e.g., Michael W. McConnell, *Active Liberty: A Progressive Alternative to Textualism and Originalism?*, 119 HARV. L. REV. 2387, 2391 (2006) (reviewing STEPHEN BREYER, *ACTIVE LIBERTY* (2005)) (“The classical liberal tradition emphasizes limited government, checks and balances, and strong protection of individual rights.”).

by pointing to some collateral gain in the quality and safety of medical decisions. Second, the incentives of self-interested individuals, acting in political settings, do not benefit from the “invisible hand” presumption that dates back to Adam Smith.¹⁰ There is no necessary alignment between public welfare and the exercise of public power, such as exists in competitive markets. The invisible-hand analogy is equally inapplicable to administrative agencies, which operate on their own internal imperatives. In many cases, the public interest might require that drugs be released on the market. Yet an agency concerned with criticism and public scrutiny will not do so, knowing that it is harder to hold it responsible for the death and pain that it did not prevent than for the death and pain that it caused. To make the point in quasi-medical terms, I have coined the term “permittitis”—the ability of government agencies to block voluntary personal decisions—which should be presumptively regarded as a danger to be avoided rather than as a progressive development worthy of social support backed by public funds.

Sound social policy places a heavy burden on any government exercise of its permit power that has such a stark impact on the lives of ordinary citizens, without their consent, and often over their protest. Even though FDA regulations are nominally directed at pharmaceutical companies, their effects are necessarily felt by the individuals who are prevented from purchasing their products. In imposing its will, the state wrongly substitutes its judgment for that of individuals. Sick people should be able to decide as a matter of right whether to assume the manifest risks of certain treatments in the hopes of receiving some greater gain.

10. Adam Smith explains the “invisible hand” presumption as follows: [E]very individual necessarily labours to render the annual revenue of the society as great as he can. He generally, indeed, neither intends to promote the public interest, nor knows how much he is promoting it. By preferring the support of domestic to that of foreign industry, he intends only his own security; and by directing that industry in such a manner as its produce may be of the greatest value, he intends only his own gain, and he is in this, as in many other cases, led by an invisible hand to promote an end which was no part of his intention. Nor is it always the worse for the society that it was no part of it. By pursuing his own interest he frequently promotes that of the society more effectually than when he really intends to promote it. I have never known much good done by those who affected to trade for the public good.

ADAM SMITH, *AN INQUIRY INTO THE NATURE AND CAUSES OF THE WEALTH OF NATIONS* 423 (Edwin Cannan ed., Random House, Inc. 1937) (1776).

To justify its assertion of power, the state must show, at a minimum, that the decisions it makes for other people are better than the decisions that they would otherwise make for themselves. Indeed, the level of improvement should be great enough to offset their loss of personal liberty—an intangible but critical value—above and beyond the administrative costs of the system. That burden is frequently met when the government seeks to control activities that may harm others, as with pollution and contagion.¹¹ The FDA, however, does not guard against harm to strangers, but only against potential harms that individuals may or may not inflict upon themselves. In this context, the threshold for government intervention should be even higher.

Any evaluation of the FDA's performance in permitting drugs and devices must examine the sources of error in both public and private decision-making. This comparison cannot be properly made if it only contrasts the knowledge of government agents with that of individual patients, even when acting under the advice of a physician. The key to any global assessment on relative institutional competence also depends on whether various private voluntary organizations—both for-profit and non-profit—serve as effective intermediaries for collecting and organizing information in ways that improve the caliber of patient treatment decisions. These intermediate organizations should not be dismissed as some social will-of-the-wisp, for they occupy a distinctive and powerful niche in virtually all areas of social life. Generally, autonomous individuals do not crave personal isolation; rather, they wish to control their own destiny in cooperation with others.¹² Getting the right forms of organization is not easy if their only interactions take place on a one-on-one basis, where the social landscape becomes even more dense. Trade and social associations often act as critical liaisons between the individual and the state, either by aggregating preferences to affect political decisions or by

11. See LAWRENCE O. GOSTIN, *PUBLIC HEALTH LAW: POWER, DUTY, RESTRAINT* 16–17 (2008) (discussing broadly the regulation of harmful activities); Mark Hall, *The Scope and Limits of Public Health Law*, 46 *PERSP. BIOL. & MED.* S199, S204–05 (Supp. 2003) (discussing the critical role of regulating pollution and contagion specifically). For a rejoinder to Gostin, see Richard A. Epstein, *In Defense of the "Old" Public Health: The Legal Framework for the Regulation of Public Health*, 69 *BROOK. L. REV.* 1421, 1425–28 (2004).

12. Cf. Epstein, *supra* note 4, at 564 (arguing that an autonomous individual is properly defined as one who has an awareness of how his or her actions affect others).

collecting information for their members.¹³ This pooling of resources generates more reliable information at a lower cost and helps to overcome coordination problems without the need for government coercion.¹⁴ That information is, of course, not perfect, which is one reason why a multiplicity of sources allows for each organization to impose its checks on the other.

Indeed, these types of intermediaries are commonplace for all serious diseases, serving as a clearinghouse for medical information.¹⁵ Many are managed by families of individuals who have suffered or died from serious diseases.¹⁶ Others are run commercially¹⁷ or by professional medical societies.¹⁸ Given the ubiquitous, long-term presence of these private institutions or patient groups, the critical question is whether a rigid state

13. See ROBERT D. REID & DAVID C. BOJANIC, *HOSPITALITY MARKETING MANAGEMENT* 214 (4th ed. 2006) (“[T]rade associations collect information from their members and then provide industry averages that can be used to measure a firm’s relative importance.”).

14. Cf. Arnold J. Rosoff, *Consumer-Driven Health Care: Questions, Cautions, and an Inconvenient Truth*, 28 J. LEGAL MED. 11, 24–25 (2007) (suggesting that as consumers become more involved in the healthcare marketplace “there will be increasing pressure on providers to make information available” and “mechanisms of various sorts, governmental and private, will evolve to assure that information is reliable and up to date”).

15. See, e.g., AMERICAN CANCER SOCIETY, *TREATMENT DECISION TOOLS* (2009), http://www.cancer.org/docroot/ETO/eto_1_1a.asp?from=fast/ (providing extensive information about various cancers and available treatments).

16. See, e.g., ALS Worldwide, <http://www.alsworldwide.org/> (last visited Oct. 21, 2009) (noting that ALS Worldwide, which deals with amyotrophic lateral sclerosis, or Lou Gehrig’s disease, was created by Stephen and Barbara Byer after losing their son to ALS).

17. See Amy P. Abernethy et al., *Systematic Review: Reliability of Compendia Methods for Off-Label Oncology Indications*, 150 ANNALS INTERNAL MED. 336, 336–37 (2009) (listing the following compendia of cancer treatment information: American Hospital Formulary Service Drug Information, United States Pharmacopeia Drug Information for the Health Professional (now known as “DrugPoints”), DRUGDEX Information System, Drug Facts and Comparisons, NCCN, and Clinical Pharmacology). The databases Abernethy lists are available only for commercial subscribers.

18. One example, the Consortium for Citizens With Disabilities, serves as a clearinghouse of information on a range of health care topics, and is comprised of nearly one hundred member organizations who operate together to advocate for national public policy measures. See Consortium for Citizens With Disabilities, <http://www.c-c-d.org> (last visited Oct. 21, 2009). Another, the International Lyme and Associated Diseases Society, provides a forum for medical professionals dedicated to the proper diagnosis and treatment of Lyme and its associated diseases through reviewing clinical research programs and providing material, advice, and education for physicians and healthcare providers. See International Lyme and Associated Diseases Society, <http://www.ilads.org> (last visited Oct. 21, 2009).

permit and certification system can outperform them where there exists an incentive to speed up delivery of accurate information about cancer therapies to their patients. I do not think that this burden can be met. The critique here is not directed toward the performance of individual officials and scientists inside the FDA, but rather to the basic structure that defines its institutional role as a comprehensive regulator. No grant of monopoly power is justified if private groups are able to provide better information to potential end users at lower costs than the state.

To make this case I proceed in several steps. Part I deals with how to analyze the two types of errors that arise in any context that requires decision-making under conditions of uncertainty. In so doing, it first identifies the costs that should be minimized and then argues that in any rational-choice environment those costs should be the sum of errors from over- and undertreatment, without regard to whether the harm in question is caused by a therapeutic agent or a natural cause. Part II uses the same imperfect cost/benefit techniques to argue that any error analysis will require that all persons, whether as regulators, physicians, or patients obtain reliable information to minimize the costs of error. Part III examines the relative case for coercive and private action. It concludes that state coercion is necessary for dealing with adulteration and counterfeiting but has little useful role in cancer cases, where information processing can be done more efficiently by a wide range of private parties. Part IV examines the underlying pattern of centralized control within the FDA and concludes that this kind of control works no better in medicine than anywhere else. Part V finishes with an examination of two major difficulties of the FDA's centralized processes, namely its inability to continuously update its decisions and its vulnerability with respect to political and economic influences. A brief conclusion follows. Conspicuously missing from this outline is the role of tort liability under either product liability or medical malpractice. The complications from these claims are legion, but one fact that defines the field is this: the precarious position of all serious cancer patients is such that the damages from tort liability are so small that pursuit of these remedies is a rarity. The regulatory system dominates the field.

I. CAUSATION AND COST/BENEFIT ANALYSIS

Any analysis of FDA procedures for evaluating drug usage must take into account the two forms of error associated with all decisions under conditions of uncertainty. Type I error, or a false positive, arises when the FDA approves a drug that causes net harm.¹⁹ Type II error, or a false negative, arises from the regulatory decision to keep drugs off the market that have a positive expected value in use for at least some identifiable set of patients.²⁰ The key point here is that FDA regulation does not occur in a vacuum. Where it keeps a drug off the market, it precludes any individualized cost/benefit analysis that patients and physicians can make as to whether to use drugs already approved for use. Where it lets a drug onto the market, this second filter still remains in place.

In working through these calculations at either stage, both the FDA and individual patients must avoid drawing philosophical, moral, or functional distinctions between any harm caused by the treatment and any caused by the disease. It is difficult to ignore that distinction in this context because it is often so relevant in other identifiable legal contexts.²¹ More specifically, the early tort law governing liability in personal injury cases concentrated on situations where one person's actions caused harm to a *stranger*, either intentionally or by inadvertence.²² Hitting other individuals or creating dangerous latent conditions are the paradigmatic illustrations of these cases.²³ For example, it matters whether a boulder that landed on a plaintiff was set in motion by natural forces or by the actions of a human being. Why? Because generally the positive law does not impose any individual duty on one person to guard

19. See RICHARD A. EPSTEIN, *OVERDOSE: HOW EXCESSIVE GOVERNMENT REGULATION STIFLES PHARMACEUTICAL INNOVATION* 116–18 (2006).

20. See *id.*

21. See Richard A. Epstein, *Medical Malpractice: The Case for Contract*, 1 AM. B. FOUND. RES. J. 87, 94–110, 122, 130 (1976); Richard A. Epstein, *The Path to The T.J. Hooper: Of Custom and Due Care*, 21 J. LEGAL STUD. 1, 4–5, 19–20 (1992). The distinction is found in many, but by no means all, cases. See, e.g., *Holland v. Pitocchelli*, 13 N.E.2d 390, 390–91 (Mass. 1938) (noting the distinction); *Farwell v. Boston & Worcester R.R.*, 45 Mass. (4 Met.) 49, 60–61 (1842) (illustrating the distinction's historical use); *Pfaffenbach v. White Plains Express Corp.*, 216 N.E.2d 324, 325–26 (N.Y. 1966) (Burke, J., concurring) (applying the distinction).

22. See generally Richard A. Epstein, *A Theory of Strict Liability*, 2 J. LEGAL STUD. 151, 166–89 (1973) (discussing the various causal paradigms in stranger cases).

23. See *id.* at 166–68, 177–79.

against natural misfortunes that befall another.²⁴ It does, however, hold any individual responsible for damages inflicted on a stranger when the defendant's conduct is not beneficial.²⁵

It should be noted, however, that the liability scheme in the stranger case is wholly inapplicable in medical treatment settings since the parties are not strangers but rather persons joined together in some special relationship. One potent reason to encourage the *deliberate* infliction of harm is the expectation that an *aggressive* response to medical threats will cause less harm than the treatment eliminates, which is why cancer patients tolerate drugs known to have dreadful side effects.²⁶ The parties' voluntary interactions in making health care decisions logically rests on their expectation of mutual benefit. To isolate the planned harms for rebuke without offsetting their associated benefits is to deny the rationality of the whole decision-making process. People undergo a course of treatment *not* to minimize the risk of a Type I error, where they could be killed or harmed by drug therapy, but rather in an attempt to minimize the *sum* of errors in both directions, no matter whether caused by natural events or by human intervention. They do so because they will only be able to reach their highest levels of personal happiness if they take both kinds of errors into account. To stress one kind of error to the exclusion of the other leads to needless sacrifices of personal satisfaction.

The failure to identify the proper goal of medical decision-making has led to serious distortions in health care policy generally. One central precept of medical ethics relates to the sovereign power that each individual has to refuse various forms of medical treatment.²⁷ No physician or government can force any competent individual, however foolish, to accept treatment against her will.²⁸ This notion is based on a social understanding that no individual should be required to take the risk, or suffer the harm, associated with the administration of medical treatment. Decisions to refuse treatment are personal. Individuals may, and usually do, seek advice from

24. See RESTATEMENT (SECOND) OF TORTS § 315 (1965); Francis H. Bohlen, *The Moral Duty to Aid Others as a Basis of Tort Liability*, 56 U. PA. L. REV. 217, 218–20 (1908).

25. See Bohlen, *supra* note 24, at 219.

26. See ABELOFF'S CLINICAL ONCOLOGY 459–81 (Martin D. Abelloff et al. eds., 4th ed. 2008) (listing side effects of various chemotherapeutic cancer drugs).

27. See Epstein, *supra* note 4, at 569.

28. See *supra* note 3 and accompanying text.

others before making their choices, but the final decision is theirs. The willingness to allow stupid decisions does not stem from the desire to expand human suffering, but from more salient considerations. Individuals have better knowledge of their own subjective preferences, which is why the modern law inclines strongly to imposing a duty to disclose on physicians so that patients can link their subjective preferences to reliable information about the consequences of various alternatives.²⁹ In addition, people will devote more attention to making the correct health care decisions when they cannot be second-guessed. After all, investments in information only yield a positive return to the extent that they are the basis of individual action. If people were certain that others would override their individual choices, any effort to get better information would be a pure waste that yielded no positive return. At that point no one would make even the simplest inquiry. By extension, the greater the likelihood that the state will override choice, the less people will invest in making responsible choices. The state should, of course, provide some protection against fraud, but in most cases the best way to do this is through lawsuits against the supplier of fraudulent information.³⁰ A decrease in permits issued by the FDA is a classic instance of regulatory overkill.

In modern health care settings, our understanding of personal autonomy is altered when the question turns to the right of any individual to *accept* medical treatment that could cause harm, alleviate suffering, or both. While the language of autonomous choice is often invoked in this discussion, the subtext is noticeably different. Commonly, proponents of FDA oversight argue that an agency or board should protect autonomous individuals of limited ability from making their own choices, lest they make too many mistakes. The legal approach slides im-

29. See *Canterbury v. Spence*, 464 F.2d 772, 790 (D.C. Cir. 1972) (“[T]he very purpose of the disclosure rule is to protect the patient against consequences which, if known, he would have avoided by foregoing the treatment.”). For a discussion of the cross-currents between objective and subjective choices, see Peter H. Schuck, *Rethinking Informed Consent*, 103 YALE L.J. 899, 956–59 (1994).

30. See, e.g., Alex Berenson, *33 States to Get \$62 Million in Zyprexa Case Settlement*, N.Y. TIMES, Oct. 7, 2008, at B7 (reporting that state-initiated lawsuits against drug company Eli Lilly for improperly marketing the antipsychotic medication Zyprexa netted the largest consumer protection settlement in history).

perceptibly but inexorably from self-determination to paternalism.³¹

Within this framework, therefore, the principle of patient autonomy accords equal weight to the right to receive drug treatment and the right to refuse it. To raise the ante for drug approval on the grounds that it is “worse” to kill than to let die goes against the basic effort to maximize the personal gains from the receipt of health care.³² The individual patient tries to minimize the sum of the two kinds of error and will adopt any strategy where the expected outcomes yield a gain that is greater than the cost of treatment. It is critical to note, however, that FDA incentives are not aligned with a patient’s expected value calculations. All agencies are subject to political pressures which occur when decisions cause traceable, *visible* harms.³³ The harms that are caused by particular therapeutic agents—such as thalidomide, which causes major limb deformities³⁴—attract immense political pressures to ban these dangerous products from the marketplace.³⁵ Overall, the result is a strong bias to overweigh Type I error relative to the quiet harms that arise when individuals die for want of therapeutic agents that languish unapproved within the FDA.

It is for this reason that many, but by no means all, patient groups tend to be more vocal than the FDA about allowing new therapies on the market.³⁶ Additionally, appeals by families to

31. See, e.g., *United States v. Rutherford*, 442 U.S. 544, 552–53 (1979) (holding that Congress passed the Food, Drug and Cosmetic Act and the 1962 Amendments to the Act in part to shield and protect terminally ill patients).

32. See EPSTEIN, *supra* note 19, at 116–18.

33. See Brief for John E. Calfee et al. as Amici Curiae Supporting Petitioner at 5, *Wyeth v. Levine*, 129 S. Ct. 1187 (2009) (No. 06-1249) (explaining that the FDA knows it faces more heat when it commits the visible Type I error of letting bad drugs on the market than the invisible Type II error of keeping good drugs off the market). As a matter of social utility, the two errors are of equal magnitude. See EPSTEIN, *supra* note 19, at 116–18.

34. See HARVEY TEFF & COLIN MUNRO, *THALIDOMIDE: THE LEGAL AFTERMATH* 4–6 (1976).

35. See *id.* at 122 (documenting President John F. Kennedy’s call for increased regulation of drugs in his 1962 State of the Union address in response to thalidomide’s dangerous side effects).

36. See, e.g., The International Myeloma Foundation, the MDS Foundation and a Coalition of Patient Advocacy Organizations Call for Updated Rules for Reimbursement, Access and Approvals for New and Existing Cancer Treatments, <http://myeloma.org/main.jsp?type=article&id=2651> (outlining a “Statement of Principles” issued on behalf of patients and caregivers demanding that policies for early approval of new cancer treatments be “reformed and streamlined” and that “an efficient and effective mechanism” be created to allow patients to access experimental treatments).

allow experimental uses of drugs that lack FDA approval are also common.³⁷ In these cases, the FDA is reluctant to allow deviation from its norms because it may undermine the usefulness of clinical trials.³⁸ Clinical trials, however, are often too little or too late for ailing individuals.³⁹ Most patients do not ask whether a new treatment meets some abstract standard of statistical significance, which says that there is a ninety-five percent chance of some positive result. They do not have that luxury. Rather, they want to know whether the new drug gives them a chance, however small, to improve their status quo.

Some measure of how this works is the sad story of Abigail Burroughs, who died of squamous cell carcinoma at age twenty-one. At this point the story runs as follows:

Not long after her diagnosis, the Burroughs family learned of an investigational cancer drug, Erbitux, that showed good response in early trials. Abigail's prominent oncologist at Johns Hopkins Hospital believed the drug had a significant chance of saving her life. But every effort on the part of her family, physician, and supporters to procure the drug for Abigail failed. She was ineligible for a clinical trial and the drug company couldn't provide her with Erbitux for compassionate use. The FDA was unmoved by her life-and-death situation.⁴⁰ Abigail died on June 9, 2001.⁴¹ On February 12, 2004, the FDA approved Erbitux "to treat patients with advanced colorectal cancer that has spread to other parts of the body."⁴²

After her death, Abigail's father, Frank Burroughs, founded the Abigail Alliance, which promptly initiated a major

37. See, e.g., Amy Harmon, *Fighting for a Last Chance at Life*, N.Y. TIMES, May 16, 2009, § 1, at 1 (documenting the struggles of one family's appeal to the FDA for the experimental use of an unapproved drug).

38. See *id.* ("The F.D.A. itself does not want patients to bypass clinical trials, which require that some patients receive a placebo to determine reliably whether a drug works.").

39. See Alexander Kamb et al., *Why Is Cancer Drug Discovery So Difficult?*, 6 NATURE REVIEWS DRUG DISCOVERY 115, 115 (2007) ("Oncology has one of the poorest records for investigational drugs in clinical development, with success rates that are more than three times lower than for cardiovascular diseases.").

40. Sue Kovach, *The Abigail Alliance Motivated by Tragic Circumstances, Families Battle an Uncaring Bureaucracy*, LIFE EXTENSION (SPECIAL EDITION), 2007, at 25, 26.

41. The Abigail Story, <http://abigail-alliance.org/story.htm> (last visited Oct. 21, 2009).

42. News Release, U.S. Food & Drug Admin., FDA Approves Erbitux for Colorectal Cancer (Feb. 12, 2004), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108244.htm>.

litigation effort to insist that the autonomy interests of individual patients give them a constitutional right to take, with or without FDA approval, any drug that has passed Stage I clinical trials.⁴³ Their proposal met an initial round of success by a three-judge panel in *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, but was ultimately and decisively quashed when the case was reheard en banc.⁴⁴ The court en banc held that FDA authority over health matters is wholly consistent with American constitutional traditions under which “the democratic branches are better suited to decide the proper balance between the uncertain risks and benefits of medical technology, and are entitled to deference in doing so.”⁴⁵

Why this deference to democratic institutions? The case does not involve the provision of any standard type of public good, and the argument is phrased with such generality that it would justify political institutions forcing technology on unwilling individuals. Moreover, it would surely require overruling decisions such as *Griswold v. Connecticut*,⁴⁶ on the ground that rights to privacy must yield to the ability of democratic institutions to decide which individuals should have access to contraceptives and why.

It is hard to sustain any close examination of the competing individual and state interests on the all too generous standard of *Abigail Alliance*. Put otherwise, the breadth of this deference claim seems to dispense with any close examination of the state interest that is put forward to limit individual autonomy. Yet any particularized review of the evidence shows the weakness of the government’s case. It is surely understandable, by way of comparison, that individuals do not have the constitutional right to assisted suicide, as the Supreme Court held in *Washington v. Glucksberg*⁴⁷ and *Vacco v. Quill*.⁴⁸ To be sure, people have a strong autonomy interest in ending their own lives when the anticipated pain is greater than any future joys from living. But there are risks as well, given the fragile competence of people in end-of-life situations and the risk of family

43. See Jerome Groopman, *The Right to a Trial*, NEW YORKER, Dec. 18, 2006, at 40, 40 (explaining the formation and goals of the Abigail Alliance).

44. *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, 445 F.3d 470, 486 (D.C. Cir. 2006), *rev’d en banc*, 495 F.3d 695, 713 (D.C. Cir. 2007); see also Epstein, *supra* note 4, at 574–76.

45. *Abigail Alliance*, 495 F.3d at 713.

46. 381 U.S. 479 (1965).

47. 521 U.S. 702, 735 (1997).

48. 521 U.S. 793, 797 (1997).

members who may prefer to bring about their early deaths. In Abigail Burroughs's case, the individual patient was seeking life, not death, and the perceived conflicts of interest among family members looked to be at a low ebb.⁴⁹ Additionally, when patients are not eligible for clinical trials there is no colorable claim that individual "opt-outs" will make it more difficult to secure accurate information about drugs, one of the constant laments of the professional clinical trial organizations.⁵⁰ And even when those difficulties arise, as they commonly do, it is a frightening prospect to think that the FDA can block individuals from seeking the treatment of their choice in order to fill its ever-expanding rolls for clinical trials. To be sure, there is always a real risk of quackery and deception in dealing with cancer treatments.⁵¹ In all cases, however, these drugs can only be used under the supervision of a physician who remains subject to the ordinary tort and administrative law remedies for touting products that are known to be useless or worse.⁵²

It should be evident, therefore, that the policy dimensions of this dispute have not been put to rest by the en banc decision in *Abigail Alliance*. The real question does not concern collective choice through legislation, but rather individual choice on matters of unique personal importance. The decision in *Abigail Alliance*, which blindly praised legislative deference, offers no instruction on how legislation should proceed.⁵³ And it undoub-

49. See Kovach, *supra* note 40, at 26–28.

50. See Expanded Availability of Investigational New Drugs Through a Parallel Track Mechanism for People With AIDS and Other HIV-Related Disease, 57 Fed. Reg. 13,250, 13,252 (Apr. 15, 1992) (explaining that "parallel track" programs that make investigational drugs accessible only to patients who do not meet the eligibility requirements for a clinical trial will not impair the clinical trial process).

51. See, e.g., *United States v. Rutherford*, 442 U.S. 544, 558 (1978) (describing how "resourceful entrepreneurs" have historically marketed fraudulent concoctions and treatments to vulnerable patients); see also Corrected En Banc Brief for the Appellees at 35–36, *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, 495 F.3d 695 (D.C. Cir. 2007) (No. 04-5350) ("The history of drug use in the nineteenth century is a history of quackery and fraud, of desperate patients throwing away their money and their health on elixirs that did everything *except* cure diseases and save lives.").

52. For a discussion of ordinary claims against physicians with respect to prescribing drugs, see Lauren Krohn, *Cause of Action Against Physician for Negligence in Prescribing Drugs Or Medicines*, in 9 CAUSES OF ACTION 1, 6–66 (Wesley H. Winborne ed., 1986).

53. See *Abigail Alliance*, 495 F.3d at 713.

tedly sidestepped the serious question of whether legislative intervention in personal precincts is justified as a matter of right.

With the constitutional battle lost in *Abigail Alliance*, the struggle has now switched to the legislative and administrative arenas. What rules should Congress and the FDA adopt with respect to experimental and off-label uses of drugs that have already been approved in some fashion? The current legal framework gives the FDA power to regulate the use of new drugs, but does not give it the power to practice medicine, which in effect facilitates off-label uses of drugs.⁵⁴ Once a drug is on the market, the FDA cannot tell physicians how to use it. Physicians rely on trial and error, without the rigor or delay of clinical trials; anecdotal information spreads fairly quickly in a bottom-up fashion, often based on hunches, which is why surveys indicate that physicians strongly favor the continuation of off-label uses.⁵⁵ This sharing of information, however, is retarded because the legal regime makes it flatly illegal for drug companies to promote any off-label uses.⁵⁶ The FDA justifies its position as follows:

Permitting Sponsors to Promote Off-Label Uses: Would diminish or eliminate incentive to study the use and obtain definitive data[;] Could result in harm to patients from unstudied uses that actually lead to bad results, or that are merely ineffective[;] Would diminish the use of evidence-based medicine[;] Could ultimately erode the efficacy standard.⁵⁷

54. See Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 (2006). For an exhaustive discussion of this issue, see Sandra H. Johnson, *Polluting Medical Judgment? False Assumptions in the Pursuit of False Claims Regarding Off-Label Prescribing*, 9 MINN. J. L. SCI. & TECH. 61, 69–70 (2008).

55. See Daniel B. Klein & Alexander Tabarrok, *Do Off-Label Drug Practices Argue Against FDA Efficacy Requirements? A Critical Analysis of Physicians' Argumentation for Initial Efficacy Requirements*, 67 AM. J. ECON. & SOC. 743, 750 (2008) ("Of 492 physicians answering the question [of whether the FDA should restrict off-label uses], 460 opposed ending the freedom to prescribe off-label.").

56. See 21 U.S.C. §§ 355(a), 331(d) (2006) (prohibiting marketing unapproved drugs); *id.* § 352(f) (defining a drug or device as "misbranded" if not properly labeled with directions for its use); see also U.S. FOOD & DRUG ADMIN., GOOD REPRINT PRACTICES FOR THE DISTRIBUTION OF MEDICAL JOURNAL ARTICLES AND MEDICAL OR SCIENTIFIC REFERENCE PUBLICATIONS ON UNAPPROVED NEW USES OF APPROVED DRUGS AND APPROVED OR CLEARED MEDICAL DEVICES (2009), <http://www.fda.gov/oc/op/goodreprint.html> ("An approved new drug that is marketed for an unapproved use is an unapproved new drug with respect to that use. An approved drug that is marketed for an unapproved use . . . is misbranded because the labeling of such drug does not include 'adequate directions for use.'") (citations omitted).

57. Janet Woodcock, *A Shift in the Regulatory Approach* (June 23, 1997) (on file with the Minnesota Law Review) (PowerPoint presentation outlining

There is a real bite to these words. Pharmaceutical companies that have so behaved have been hit with heavy fines, including a settlement of \$455 million for Pfizer⁵⁸ and a \$700 million settlement fee on Serono Labs.⁵⁹ In addition to being liable for their own off-label promotion, pharmaceutical companies may be held liable for assisting the generic makers in their promotion of a drug's off-label use.⁶⁰ These are not trivial exposures.

The legal situation with drugs that have yet to be approved is quite different because physicians are unable to use an unapproved drug as a therapy, as was the case with Abigail Burroughs.⁶¹ Patients face stark challenges in obtaining these unapproved drugs, including the possibility of enrolling in clinical trials where they may receive a placebo instead of the drug or seeking a compassionate use exemption from the FDA to use an unapproved drug on an experimental basis.⁶² Compassionate use exemptions are exceedingly difficult to obtain because the

the reasons for FDA policies on off-label uses); *see also* Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64,074, 64,081 (Dec. 3, 1997) (describing how banning promotion of unapproved uses "protect[s] the public health by preserving the integrity of the premarket approval process" and maintains an incentive for manufacturers to conduct clinical investigations, thus "encouraging scientific research and eliminating unnecessary harms to patients"); On Biostatistics and Clinical Trial, <http://onbiostatistics.blogspot.com/2009/02/evidence-based-medicine-evidence-gap.html> (Feb. 14, 2009, 15:27 EST) (explaining the FDA's rationale for prohibiting promotion of off-label uses). *See generally* David L. Sackett et al., *Evidence Based Medicine: What It Is and What It Isn't*, 312 BRIT. MED. J. 71 (1996) (discussing the usefulness of and fears associated with the practice of evidence-based medicine).

58. *See* Johnson, *supra* note 54, at 114 (describing how the pharmaceutical company Parke-Davis paid over \$455 million as a result of litigation concerning the drug Neurontin). Parke-Davis was a division of Warner-Lambert, which later merged with Pfizer. *Id.* at 103 n.169.

59. Press Release, U.S. Dep't of Justice, Serono to Pay \$704 Million for the Illegal Marketing of AIDS Drug (Oct. 17, 2005), *available at* http://justice.gov/opa/pr/2005/October/05_civ_545.html. For a discussion of some of the First Amendment issues arising from FDA restriction of pharmaceutical promotion to physicians, *see* Aaron S. Kesselheim & Jerry Avorn, *Pharmaceutical Promotion to Physicians and First Amendment Rights*, 358 NEW ENG. J. MED. 1727, 1727-28 (2008).

60. Amaris Elliott-Engel, *Drug Companies on the Hook for Off-Label Use of Generic*, LEGAL INTELLIGENCER, Mar. 24, 2008, <http://www.law.com/jsp/pa/PubArticlePA.jsp?id=900005506685>.

61. *See* Kovach, *supra* note 40, at 26-27.

62. *See* AMERICAN CANCER SOCIETY, COMPASSIONATE DRUG USE (2009), http://www.cancer.org/docroot/ETO/content/ETO_1_2x_Compassionate_Drug_Use.asp.

FDA can impose all sorts of preconditions which take months or years to satisfy.⁶³ Drug companies often impose additional hurdles to the availability of these unapproved drugs because they are worried about tort liability and their ability to recover the costs for the new treatments.

One recent illustration of this tortuous process involves the long battle over the use of the drug Iplex, which was believed to relieve some symptoms of amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease.⁶⁴ The *New York Times* recently chronicled the efforts of Joshua Thompson's family to gain access to the drug Iplex.⁶⁵ Iplex was not immediately available to the public due to a patent dispute between Inmed and Genentech.⁶⁶ Other drug choices, however, were limited because the FDA only had one approved drug on the market for ALS, with limited effectiveness, and another drug possibly scheduled for clinical trials.⁶⁷ Thompson was only able to procure a drug similar to Iplex, and only after difficulty. One doctor, for example, refused to prescribe it because of the risk of hypoglycemia, or low blood sugar.⁶⁸ Nonetheless, Thompson wanted to try Iplex based on positive reports.⁶⁹ Some doctors backed Thompson's choice, but the issue quickly became a public administrative nightmare in which the FDA initially denied permission before finally relenting in April 2009.⁷⁰ By then, Thompson had contracted pneumonia and was put on a ventilator, which often marks the beginning of the end. Iplex, unfortunately, cannot reverse any prior deterioration.⁷¹ Better late than never does not make late better than early.

Iplex may be a dead end. Life is lived, however, going forward, which makes the correct question whether state intervention improved Thompson's odds of survival. That question involves a delicate valuation on different states of disease and hard judgments on the probability of divergent outcomes. The answer to this question does not tip the balance back toward the FDA permit system, for it is still the case that harms in-

63. See *id.* (describing requirements for access to unapproved new cancer drugs outside of a clinical trial).

64. See Harmon, *supra* note 37.

65. *Id.*

66. *Id.*

67. *Id.*

68. *Id.*

69. *Id.*

70. *Id.*

71. *Id.*

flicted by medical treatment are no more deadly than those inflicted by nature. Individual patients, in consultation with their physicians, undoubtedly make a raft of key decisions about their course of treatment. If patients are capable of making choices among a variety of approved treatments, why should they be deprived of the right to make that choice among the class of treatments that have not been approved?

One frequent objection is that desperate patients could be swayed by false optimism or bad information, perhaps through advertisements.⁷² I took the position in a recent *Wall Street Journal* editorial that once drugs pass through Phase I trials (which are intended to deal with matters of toxicity), patients should then be free to take any drug combination they choose, even if they have not gone through the more extensive Phase II and Phase III trials (which are intended to deal with matters of efficacy).⁷³ The column elicited comments from many who were frustrated with the current system⁷⁴ and the use of the Phase I

72. See MARCIA ANGELL, *THE TRUTH ABOUT THE DRUG COMPANIES: HOW THEY DECEIVE US AND WHAT TO DO ABOUT IT* 135–55 (2004) (discussing the conflict of interest inherent in drug companies' advertising and educating others about their own products); JEROME KASSIRER, *ON THE TAKE: HOW MEDICINE'S COMPLICITY WITH BIG BUSINESS CAN ENDANGER YOUR HEALTH* 50–63, 79–103 (2004) (discussing conflicts of interest); Troyen A. Brennan et al., *Health Industry Practices that Create Conflicts of Interest: A Policy Proposal for Academic Medical Centers*, 295 J. AM. MED. ASS'N 429, 431–32 (2006) (proposing heightened conflict of interest standards). For a critique of strong conflict of interest proposals, see Richard A. Epstein, *Conflicts of Interest in Health Care: Who Guards the Guardians*, 50 PERSP. BIOL. & MED. 72, 83–86 (2007) (asserting that regulators also face conflicts of interest and arguing against overregulating conflicts of interest); Thomas Stossel, *Regulation of Financial Conflicts of Interest in Medical Practice and Medical Research: A Damaging Solution in Search of a Problem*, 50 PERSP. BIOL. & MED. 54, 67–69 (2007) (attacking overreactions to conflicts of interest).

73. Richard A. Epstein, Op-Ed., *Cancer Patients Deserve Faster Access to Life-Saving Drugs*, WALL ST. J., May 2, 2009, at A1.

74. Typical of the reaction was Dr. Mark Fesen, who wrote:

As an oncologist in private practice, I encounter situations similar to this daily. In our group, we try to aggressively advocate for our patients. The bureaucratic roadblocks that we frequently run into can be deadly serious for patients and disheartening for the staff.

One recent case involved a patient who is currently in pain suffering from a metastatic small bowel cancer. The several drugs approved and tested for colon cancer (Avastin, Erbitux, Camptosar, and Oxaliplatin) have and will not and will not [sic] be tested for this rare type of cancer. Yet it makes intuitive sense to consider using them. Due to the lack of clinical trials studying these drugs in this situation, Medicare will not approve their use. NCCN guidelines, which follow evidence-based medicine and clinical trials, are of little help in this situation. Unfortunately, this patient, along with many others will

filter, designed to weed out drugs with exceedingly high toxicities. Some readers who had experience with the FDA went even further, contending that the FDA should lose its ability to issue permits.⁷⁵ I do not categorically disagree with their position.

For the moment, at least, I would leave in place the requirement that a drug pass Phase I trials. If that system works well, then perhaps even the Phase I trials could be eliminated, thereby demoting the FDA to a certifying agency without licensing authority. Alternatively, if the expanded realm of patient choice produces serious problems, it should be possible to dial back individual choice to control abuse. Exactly how this approach would work in various contexts cannot be confidently predicted in the abstract; maintaining the status quo, however, carries with it substantial risks as well. The best approach is to start small and to continuously work to expand individual choice if patient access to drugs that have passed Phase I trials produces no sign of systematic abuse.

pass away while suffering from a cancer for which useful treatment is likely very near. My patients' only option is to risk self paying for these expensive drugs.

E-mail from Dr. Mark Fesen, M.D., to author (May 3, 2009, 21:26 CDT) (on file with author).

75. Here is one such email:

As someone whose first husband died of cancer at age 40 (stomach cancer caught after it had metastasized to the liver), I appreciated your identifying much of what we went through, but I question the implied premise that the FDA should have any role in medicine. For instance, I would like to address your statement: "no one thinks that unapproved cancer drugs should be freely available to patients."

We knew that my husband's cancer was in all likelihood terminal, but it would have been far better to have had access to some drugs in the experimental stage than be told, as we were, to join the long waiting list for a clinical trial, which we did. By the time my husband's name moved to the top of the list months later, he was too weak to travel to Texas where the study was being done. He died a few weeks later.

From your article, I believe you understand how devastating this situation was to my husband and his family. But if government increases its role in the health care decisions of all Americans, this kind of story will not be a rarity. Advocating "tweaks" in the present system will not suffice; it is the basic idea of government regulating medicine that must be addressed.

The answer to our health care situation is to get the government out of the health care business and institute a completely free-market approach, getting rid of mandates and regulations that make the present system less than optimal in some cases, and disastrous in others. I hope you will consider arguments made by people like Paul Hsieh (www.WeStandFirm.org) in your thinking on this subject.

E-mail from anonymous reader to author (May 4, 2009, 15:25 CDT) (on file with author).

The argument for expanded patient choice rests on the proposition that the system already supports personal autonomy in healthcare. Quite simply, identical risks arise when individual physicians and patients are forced, as they always are, to make choices among lawful therapies. Do sufferers of prostate cancer prefer radiation, surgery, chemotherapy, pellets, or some combination thereof?⁷⁶ No one argues that the power of choice should be withdrawn from individual patients because of the distinct possibility that they will erroneously exercise it. The usual response is to counsel prudence in making private decisions, or, more dubiously, to impose procedural hurdles—such as counseling—before allowing individuals to make certain decisions. The response is not to ban the ability to make those decisions. It is a mistake to throw out the baby with the bathwater by assuming that personal imperfections in decision-making require a collective decision to disallow certain drugs from entering the market. The combination of institutional diligence, procedural safeguards, and self-help is the preferred response.

II. GATHERING GOOD INFORMATION

The need to make decisions under conditions of uncertainty is especially critical in cancer cases, where the costs of error are measured in life-and-death terms. Time is of the essence in responding to tumor growth; the earlier the time of detection, the likelier the prospects of beneficial treatment.⁷⁷ At the same time, the high toxicity of most cancer agents means that the use of the wrong compound or drug (or the wrong dosages of the right compound) could lead to either serious discomfort, earlier death, or both.⁷⁸ The upside of proper treatment is usually low because curing certain cancers may well be a remote possibility. Frequently, the patient's best hope is to prolong her life by years or even months, and perhaps, but not necessarily, improve her quality of life. Any insistence that approved cancer drugs will result in a complete cure would make the best the enemy of the good, given that perfection is unattainable. Not even the FDA insists on that. Usual treatment protocols call for the use of multiple drugs in sequence, starting with the least

76. See ABELOFF'S CLINICAL ONCOLOGY, *supra* note 26, at 1667–80 (describing various prostate cancer treatments).

77. *Id.* at 361.

78. See *id.* at 459–81 (discussing chemotherapeutic drugs and their known toxicities, or side effects).

toxic drug, and when that treatment starts to falter, stronger agents are tried in turn until the drug cabinet is empty.⁷⁹ Physicians know this, of course, and there is little risk that they will leapfrog to risky drugs when conventional therapies have not yet been tried.

The grim prospect of most cancer treatment options is, however, not improved by FDA regulation. Cancer patients are precariously perched on the unhappy horns of an inescapable dilemma: the high costs of inaction, often resulting in death, versus the high costs of action, often resulting in faster death or serious distress. A patient's decisions involve high rates of error in both directions, where each error carries a high expected loss. Yet however bleak the prospects, the same methodology applies: maximize expected value in deciding on a course of treatment, if any. Therefore, one defensible option is hospice care without treatment, when all the alternatives look worse.⁸⁰ In making these decisions, *reliable information really matters* because the illogical strategy is to base decisions solely on the casual accretion of information. A small reduction in the probability of an adverse outcome or short remission from treatment could produce enormous improvements in either the quality or length of life.

The question is often whether improvement in outcomes for the individual (and through that person, for society) is greater than the costs of obtaining better information. With most naïve patients, the answer is so clearly yes that no cancer patient relies on his or her own judgment to decide which course of therapy or nontherapy to follow. The operative inquiry should be, and often is, whether further investment in information costs less than the gain from any anticipated reduction in error costs. Since the answer is often yes, how should we organize our systems of social control to maximize the rate of return from private investments in additional information, given the high value of human life?⁸¹

79. See *id.* at 451.

80. See AMERICAN CANCER SOCIETY, WHAT IS HOSPICE CARE? (2009), http://www.cancer.org/docroot/ETO/content/ETO_2_5x_What_Is_Hospice_Care.asp ("Hospice care is meant for the time when cancer treatment can no longer help you.").

81. One general conceit states that a human being should be treated as a "six million dollar man." See Kevin Murphy & Robert Topel, *Diminishing Returns?: The Costs and Benefits of Improving Health*, 46 PERSP. BIOL. & MED. S108, S110–15 (2003) (calculating the value of increasing longevity). There are many complications here, including questions of the sensitivity of the value of

III. GOVERNMENT MONOPOLY VERSUS VOLUNTARY INTERMEDIARIES

The central issue, therefore, is whether the government, voluntary institutions, or both, should be used to overcome the pervasive information shortfalls on drug treatments. I think that the answer here is clear. 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.

In this new scenario, the FDA retains a key role in protecting public health, but has little responsibility in approving or disapproving cancer therapies. A powerful state presence is needed, for example, to insure the health and safety of the public at large. The FDA should focus its resources on the rash of contaminated food that has poured in from overseas and on the extensive counterfeiting rings that seek to inject defective foods and drugs into this nation's distribution pipeline.⁸² Honest manufacturers will go to enormous lengths by themselves to protect their brands against perceived defects in quality, as Johnson & Johnson did in recalling Tylenol after someone laced its tablets with cyanide.⁸³ These private efforts must be backed by government regulations that can impose criminal sanctions on various malefactors who try to sell dangerous or purloined goods. Indeed, private manufacturers often welcome and adver-

life to age and health conditions, but the revealed behavior suggests a high number. The precise number does not matter so long as it is large. But the size of the information gap sets in motion a set of private and public strategies toward data collection that shape the social organization for the provision of cancer treatment. Improve odds by five percent and, as a first approximation, there is substantial social gain, which if not \$300,000, is still substantial. *See id.* at S111. With error costs high and mistakes common, it makes sense for everyone to invest heavily in knowledge.

82. *See, e.g.,* Robert Cockburn et al., *The Global Threat of Counterfeit Drugs: Why Industry and Governments Must Communicate the Dangers*, 4 PUB. LIBR. SCI. MED. 302, 302–08 (2005) (discussing why the government has to counteract the risk of counterfeit drugs); Paul M. Rudolf & Ilisa B.G. Bernstein, *Counterfeit Drugs*, 350 NEW ENG. J. MED. 1384, 1384–86 (2004) (noting the rising incidence of counterfeit drugs). The process has world-wide implications. *See* Roger Bate, *New Tools to Fight Fake Medicines*, AM. ENTERPRISE INST. FOR PUB. POL'Y RES., May 13, 2009, <http://www.aei.org/article/100492>.

83. Mallenbaker.net, *Companies in Crisis—What to Do When It All Goes Wrong*, <http://www.mallenbaker.net/csr/crisis02.html> (last visited Oct. 21, 2009) (recounting the response to incidents in 1982 and 1986 when seven people died in Chicago after consuming cyanide-laced Tylenol, causing a loss of one billion dollars in market value after the 1982 incident and spurring wide recalls and the creation of tamper proof packages after the 1986 incident).

tise “FDA-approval” to increase consumer confidence in their products.⁸⁴

Drug treatments relating to oncology, however, are unrelated to matters of drug purity or consumer confidence. The distribution of cancer drugs does not require the FDA to strengthen public communication, as might be required for those drugs that large numbers of ordinary individuals take on a regular basis.⁸⁵ In contrast, oncology drugs are distributed through restricted channels and only to people who understand how and why they are administered.⁸⁶ In instances of cancer, patients and their doctors must assemble information to understand the tradeoffs on the safety and the effectiveness of drugs in their own individual cases. It is politically unwise to give *any* agency, however skilled or competent, monopoly control over whether people may use a particular drug or therapy when it lacks the individualized calculation of whether, for example, patients have risk factors for particular treatments. Indeed, if the FDA rejects a new drug application, the product or service may not be sold at all, which necessarily has high Type II error costs. Even if the FDA allows the drug to be marketed, it can subject it to various conditions that relate to pricing, advertising, and permissible users, among others, which can limit its dissemination and use.⁸⁷ Additional

84. See U.S. Food & Drug Admin., Is It Really FDA Approved?, <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm047470.htm#biologics> (last visited Oct. 21, 2009) (noting some manufacturers may say their products are “FDA-approved”).

85. Cf. Posting of Peter Pitts to DrugWonks.com, http://www.drugwonks.com/blog_post/show/4755 (Feb. 28, 2008, 10:58 EST) (describing the FDA Commissioner’s remarks about how clear FDA communication combats the erosion of consumer trust).

86. See, e.g., American Cancer Society, FDA Approves Advanced Prostate Cancer Drug, Dec. 2, 2003, http://www.cancer.org/docroot/NWS/content/NWS_2_1x_FDA_Approves_Advanced_Prostate_Cancer_Drug.asp (describing a cancer drug that can only be prescribed by a limited number of doctors due to its serious side effects).

87. Recently, the FDA has demanded a “Risk Evaluation and Mitigation Strategy,” or “REMS,” in some circumstances. That requirement could undermine the present legal framework that allows doctors to make off-label uses of drugs. See U.S. Food & Drug Admin., Questions and Answers on the Federal Register Notice on Drugs and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies, <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendments/totheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095439.htm> (last visited Oct. 21, 2009) (explaining the Identification of Drug and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies

requests for new data or to conduct additional clinical tests breed further delay, which both raises treatment costs and leads people to forego the drug's use.⁸⁸ Warnings of negative side effects, for example, are calculated to lower the expectations of potential users. The concerns here are not hypothetical, for just this pattern emerged with Prozac,⁸⁹ where decreased use for treating teenage and young adult depression is highly correlated with warnings about increases in the suicidal behavior that Prozac allegedly causes.⁹⁰

One implicit but incorrect assumption is that FDA competence must be compared with the joint knowledge of an individual patient and his or her physician, both of which could prove to be limited. Defenders of the FDA are right to point out that collective generation of the information is usually superior to individual impressions.⁹¹ They are wrong, however, to assume that government agencies are the only bodies that can assemble and interpret the relevant information. It is more advisable to compare the FDA to voluntary associations, including those that deal with oncology.⁹² Individual patients and physi-

for Purposes of the Food and Drug Administration Amendments Act of 2007, 73 Fed. Reg. 16,313, at 16,313 (Mar. 27, 2008)).

88. See *The Law of Biologic Medicine: Hearing Before the S. Comm. on the Judiciary*, 108th Cong. 122–35 (2004) (submission of Lester M. Crawford, Acting Comm'r of Food & Drugs, Dep't of Health & Human Servs.) (noting that faster FDA approval of drugs reduces their cost and increases their availability).

89. See, e.g., PHYSICIANS' DESK REFERENCE 1852 (63d ed. 2009) (describing Prozac as an antidepressant that functions as a selective serotonin reuptake inhibitor (SSRI), which blocks the absorption of serotonin into the blood).

90. The abstract of one study states the following conclusion:

SSRI prescriptions for youths decreased by approximately 22% in both the United States and the Netherlands after the warnings were issued. In the Netherlands, the youth suicide rate increased by 49% between 2003 and 2005 and shows a significant inverse association with SSRI prescriptions. In the United States, youth suicide rates increased by 14% between 2003 and 2004, which is the largest year-to-year change in suicide rates in this population since the Centers for Disease Control and Prevention began systematically collecting suicide data in 1979.

Robert D. Gibbons et al., *Early Evidence on the Effects of Regulators' Suicidal-ity Warnings on SSRI Prescriptions and Suicide in Children and Adolescents*, 164 AM. J. PSYCHIATRY 1356, 1356 (2007).

91. See Arnold S. Relman, *To Lose Trust, Every Day*, NEW REPUBLIC, July 23, 2007, at 36, 40 (2007) (reviewing EPSTEIN, *supra* note 19).

92. Cf. Reed Abelson & Andrew Pollack, *Medicare Widens Drugs It Accepts for Cancer Care*, N.Y. TIMES, Jan. 27, 2009, at A1 (discussing new policies regarding the FDA's use of recommendations from voluntary organizations).

cians *already* rely on these voluntary organizations to serve as intermediaries between them and the manufacturers or sellers of cancer drugs for medications that are licensed for particular uses.⁹³ There is no reason why their role cannot be extended.

To understand why, recall that voluntary organizations are not whimsical creations. Indeed they are fixtures in many contexts that are unrelated to cancer or medicine.⁹⁴ They are typically nonprofit organizations that serve the same basic intermediation function in virtually all markets: to collect, digest, and interpret material for their members in areas where there is an information shortfall. They set best practice standards and convey these standards to their membership on a national and global level, so that doctors in the United States can benefit from information obtained from Europe or Asia.⁹⁵ Unlike government monopolies, these organizations operate by persuasion, not coercion,⁹⁶ and they act in competition with each other. Participating physician members use information from such organizations as they will, knowing that they can report their own experiences back to the standing body in a conscious and continuous feedback loop. If one organization falters, as can easily happen, others pick up the slack.⁹⁷ So long as there is no monopoly control, physicians can search out the best sources of information.⁹⁸

These groups are formed with respect to virtually every specialty, which in turn is broken down by subspecialties. They have budgets,⁹⁹ organized subcommittees,¹⁰⁰ extensive websites,¹⁰¹ clear missions,¹⁰² and a proven ability to quickly com-

93. *See id.*

94. *See* NATIONAL TRADE AND PROFESSIONAL ASSOCIATIONS OF THE UNITED STATES, at i–viii (Valerie S. Sheridan ed., Columbia Books, 43d ed. 2008), for a list of over 7600 trade associations in the United States, many of which serve multiple functions.

95. *See id.* at ii (noting international cooperation).

96. *See id.* at iii (“Both membership and donor-based organizations are heavily reliant on public trust . . .”).

97. *See* Abelson & Pollack, *supra* note 92 (noting the use of alternative references).

98. *Cf. id.* (giving examples of various sources of information).

99. *See id.* (describing the funding systems of some groups).

100. *See id.* (noting the steps taken to control conflicts of interest within committees).

101. *See, e.g.,* American Chronic Pain Association, <http://www.theacpa.org/> (last visited Oct. 21, 2009).

102. For an example of one voluntary organization’s mission statement, *see id.*

pile complex information.¹⁰³ And they work hard to make their databases interactive.¹⁰⁴ The gains from creating these intermediaries evidently dwarf the transaction costs needed to put these groups together: if that were not the case, these groups would not be so widespread. Within medicine they can supply information the FDA is too hidebound to collect and disseminate. They can also go further than making a simple judgment of whether to license by recommending the proper sequence for the use of various cancer treatments that distinguishes first-line treatments from those of last resort.

These intermediate institutions assume special importance because of the peculiar structure of U.S. food and drug laws, which create a sharp distinction between on-label drug uses that the manufacturer can promote and off-label drug uses that manufacturers cannot promote, even if they use information that was published and disseminated in established journals.¹⁰⁵ The current legal landscape thus creates an unfortunate legal no-man's-land. If a drug is not approved for any use at all, then patients cannot use it to treat any ailment. Physicians may still learn about these unapproved drugs from the limited information released about the outcomes of clinical trials. Once a drug is approved for one use, however, the decision over off-label uses lies within the ambit of physicians and hospitals, given that the FDA cannot regulate medical practice.¹⁰⁶

103. See Abelson & Pollack, *supra* note 92 (stating that Medicare's new policy of using recommendations from more voluntary organizations is partly in response to concerns that "the agency has been too slow to recognize promising new off-label treatments").

104. See, e.g., Society of Thoracic Surgeons, Welcome to the STS National Database, <http://www.sts.org/sections/stsnationaldatabase/> (last visited Oct. 21, 2009).

105. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 352 (2006) (regulating drug labeling); see also *United States v. Caronia*, 576 F. Supp. 2d 385, 392 (E.D.N.Y. 2008) ("It is well established that under the FDA's 'intended use' regulations, the promotion of a drug for an off-label use by the manufacturer or its representative is prohibited regardless of what directions the manufacturer or representative may give for that use."). See generally Johnson, *supra* note 54, at 81–83 (discussing some of the difficulties surrounding the regulation of off-label drug use).

106. U.S. Food & Drug Admin., Questions and Answers: Problem Reporting, <http://www.fda.gov/Safety/ReportaProblem/QuestionsandAnswersProblemReporting/default.htm#problems> (last visited Oct. 21, 2009) (noting "medical practice" is not handled by the FDA).

Off-label uses are a staple of cancer treatment.¹⁰⁷ Clinical trials are extremely expensive and the FDA, under Congressional prodding, continues to add requirements that increase the size of the patient cohort and the various subdivisions within it.¹⁰⁸ Consequently, drug owners are reluctant to run clinical trials for new indications—i.e. different types of tumors—while physicians are reluctant to include patients in clinical trials.¹⁰⁹ It becomes troublesome, and almost immoral, to subject very sick individuals to clinical trials when the available evidence, however sketchy, suggests that off-label use is likely more advantageous than standard treatments that have been tried and have failed. Strong reasons back patients' reluctance to participate in clinical trials for off-label uses. First, patients are often unwilling or unable to participate in trials because their odds of getting a placebo during the clinical trial are quite high, often between thirty-three and fifty percent.¹¹⁰

Some estimates, however, indicate that over half of the prescription medications provided to patients in the United States may be prescribed for a purpose, in a higher or lower dose, over a longer period of time, or for a population (such as children) different from that for which the drug has been approved.¹¹¹

Second, manufactures have no financial incentive to undertake trials. A standard drug or treatment has a limited patent life that starts to run long before commercialization.¹¹² Typically, off-label uses proliferate through clinical trials only in rare circumstances—such as using Thalidomide for treating multiple myeloma.¹¹³ The accumulation of information about off-label uses takes additional time during which the patent clock keeps running. Why should any patentee spend a fortune on clinical

107. See American Cancer Society, Off-Label Drug Use, http://www.cancer.org/docroot/ETO/content/ETO_1_2x_Off-Label_Drug_Use.asp (last visited Oct. 21, 2009) ("Off-label drug use is very common in cancer treatment.").

108. See Steve Usdin, *Regulation: System Reset in 2008*, BIOCENTURY, Jan. 21, 2008, at A1, A3–A4.

109. See *id.* (discussing how costs of the clinical trial scheme dissuade drug development).

110. See Sharona Hoffman, *The Use of Placebos in Clinical Trials: Responsible Research or Unethical Practice?*, 33 CONN. L. REV. 449, 453 (2000).

111. Johnson, *supra* note 54, at 61 (citations omitted).

112. See Margaret Gilhooly, *Drug Preemption and the Need to Reform the FDA Consultation Process*, 34 AM. J.L. & MED. 539, 552 (2008) ("Manufacturers are concerned about the limited patent life of their drugs and the need to recoup the considerable cost of drug testing within a limited time frame.").

113. See Miranda Hitti, *Thalidomide OK'd for Multiple Myeloma*, WEBMD HEALTH NEWS, May 26, 2006, <http://www.webmd.com/mental-health/bulimia-nervosa/news/20060526/thalidomide-okd-for-multiple-myeloma>.

trials for a drug that will go generic shortly after the clinical trials are completed? Notwithstanding these difficulties, the off-label uses of cancer drugs do *not* fall into a void, for there is an exhaustive physician-driven literature that studies off-label uses of particular drugs. This extensive literature is routinely correlated by intermediate agencies that publish the information. The quality of these reviews is often less than ideal. A study by Amy Abernethy and colleagues reviews six such compendia¹¹⁴ and notes serious gaps within the individual sources and obvious room for improvement.¹¹⁵

Nonetheless, the shortfalls of one publication can be offset by information obtainable from another source, since physicians can consult multiple references. The existence of gaps in any one source does not necessarily lead to a parallel gap for physicians. In addition, any new entry could, of course, improve matters. After the publication of her study, Abernethy noted that she did not oppose the decision of Medicare to reimburse for off-label uses.¹¹⁶ Indeed in some cases the resources from individual sites are impressive. The National Comprehensive Cancer Network (NCCN) maintains a wide-ranging website that offers extensive information about clinical practice guidelines for various cancers, including off-label uses.¹¹⁷ Readers of the NCCN website can find breast cancer guidelines that offer insights on how to treat inflammatory breast cancer, which is described as both “rare” and “aggressive.”¹¹⁸ The use of the words “rare” and “aggressive” indicates the importance of the voluntary transmission of information. Aggressive cancers obviously need attention, but physicians who practice away from major medical centers would necessarily struggle to gather information about these rare conditions. A national (or even global) network can better accumulate information on rare diseases by publishing resources more rapidly than any federal agency.

114. See Abernethy et al., *supra* note 17, at 336.

115. *Id.* at 341–42.

116. Interestingly enough, despite her reservations, Dr. Abernethy noted more recently that she did not oppose the new Medicare rules and cited new entry into the market as her reason. See Abelson & Pollack, *supra* note 92 (“I think the addition of the new compendia this year is an important increase in the bandwidth.” (quoting Dr. Abernethy)).

117. National Comprehensive Cancer Network, <http://www.nccn.org> (last visited Oct. 21, 2009).

118. Press Release, Nat’l Comprehensive Cancer Network, NCCN Updates Breast Cancer Guidelines (Jan. 22, 2008), available at http://www.nccn.org/about/news/archived_news.asp (follow “2008” hyperlink; then follow “NCCN Updates Breast Cancer Guidelines” hyperlink).

Does it matter that these extensive off-label uses do not meet the FDA standards? It would if we were confident that centralized government science outperforms voluntary organizations. But there is no evidence to support that conclusion. Today's fractured system of regulation, part coercive and part voluntary, arises from the fact that the FDA is not organized to supply information on a continuous basis that keeps pace with medical advances. Indeed nothing is more common, even for a lawyer, than to hear physicians decry—but always off the record—that FDA protocols, warnings and guidelines have “nothing to do” with good medical practice.¹¹⁹ It is not a healthy institutional situation for serious physicians to believe that the FDA retards medical research by—to give the common number I have heard—between three and five years.¹²⁰

These cautionary signs are not always heeded. Even today many medical experts champion full-scale clinical trials before allowing drugs into general use.¹²¹ In doing so, however, they misconceive the full nature of the problem. No one, of course, wants to ban clinical trials. Nonetheless, palpable difficulties arise in insisting that clinical trials should be strictly required for all new drug uses. Trials often start at inconvenient times for patients and patients lack options if trials are not open; think back to Abigail Burroughs.¹²² “Reliable” information also is, in Churchill's words, “too little, too late”¹²³ for a cancer patient whose options have run dry. A quick and dirty treatment often offers the best chance of survival.

In light of these considerations, our proper focus should be on how much a patient has to forego for the “privilege” of par-

119. See Richard A. Epstein, *The Case for Field Preemption of State Laws in Drug Cases*, 103 NW. U. L. REV. 463, 471 (2009) (“[T]he physician is in the best position to determine if a treatment that is undesirable in some patients is desirable in others . . .”).

120. See INST. OF MED. OF THE NAT'L ACADS., *THE FUTURE OF DRUG SAFETY* 31–64 (Alina Bacin et al. eds., 2007) (describing the drug regulatory process).

121. Thus I have been chastised as follows:

Does Epstein really not understand that properly designed and conducted clinical trials are now universally accepted as the most reliable means of determining the effectiveness of a drug? . . .

. . . .

Clinical trials . . . changed the basis for the use of drugs from something akin to hearsay and witchcraft to something much closer to science. . . .

Relman, *supra* note 91, at 40.

122. See *supra* notes 40–42 and accompanying text.

123. EUGENE L. RASOR, WINSTON S. CHURCHILL, 1874–1965, at 261 (2000).

ticipating in a clinical trial. Those costs necessarily decrease in light of the alternative avenues used to obtain information through the NCCN or similar organizations. In particular, it would be instructive to learn which off-label uses were modified or discontinued given their poor performance or, alternatively, what are the performance levels of off-label uses that have worked their way into common practice without going through clinical trials. Another useful study would compare the reliability of information disseminated about a drug's on-label and off-label use, to see if the frequency of adverse events from the off-label use exceeds those from any permitted use. Off-label uses are only for drugs that have already passed Phase I clinical trials, so that high toxicity is not a risk. *Accumulated* information for off-label uses could prove more reliable than clinical trials. I suspect that off-label uses are about as effective and safe as the on-label uses. If that hypothesis should prove true, it undermines the argument that clinical trials are the gold standard for measuring safety and effectiveness. If the hypothesis were false, then there would be a slow and steady decline in off-label uses, which does not appear to be occurring.

IV. CENTRALIZED VERSUS DECENTRALIZED KNOWLEDGE

We are now in a position to step back from the particulars of this dispute to examine the larger questions of the proper theory of knowledge acquisition. The current FDA clinical trial model reflects a belief in top-down knowledge, a theory which prefers the centralized collection and evaluation of information over decentralized methods. In effect, the FDA represents a modern central-planning paradigm of the sort that F.A. Hayek effectively criticized when socialism was at its height.¹²⁴ Single sources of control lack the redundancy to correct error, stifle the initiative that makes for advantages, and cannot coordinate and assemble information that is held in discrete packets by private individuals.

124. F. A. Hayek, *Socialist Calculation: The Competitive 'Solution,'* 7 *ECONOMICA* 125, 125–27 (1940); F. A. Hayek, *The Use of Knowledge in Society*, 35 *AM. ECON. REV.* 519, 524 (1945). For my approach to limited knowledge, see generally Richard A. Epstein, *Intuition, Custom, and Protocol: How to Make Sound Decisions with Limited Knowledge*, 2 *N.Y.U. J.L. & LIBERTY* 1 (2006) (discussing how intuition, custom, and protocol create knowledge) and Richard A. Epstein, *The Uses and Limits of Local Knowledge: A Cautionary Note on Hayek*, 1 *N.Y.U. J.L. & LIBERTY* 205 (2005) (contrasting local and formal knowledge).

There is ample reason to think that Hayek's diagnosis accurately captures the lumbering condition of today's FDA. The FDA's defenders note that even the recent statutory reforms¹²⁵ have left the FDA "chronically under-funded,"¹²⁶ particularly with respect to postmarketing surveillance. Officials worry that the rise of new scientific fields and techniques will quickly supersede the abilities of the FDA.¹²⁷ Commonly, Congress responds to these rigidities with budgetary, rather than structural, solutions. Accordingly, the usual response attacks "inadequate funding" by asking for more,¹²⁸ only to find that their prayers have been answered by the Obama administration.¹²⁹ Increased funding to protect the food supply is welcome, but funding to test for safer medical products could easily be counterproductive by slowing down the introduction of new products into the market. The fundamental question is never asked: whether *any* centralized agency can be nimble enough to process information. On this score the dismal history of central planning in every other sector of the economy suggests that serious improvements cannot be reached by putting the FDA on steroids. Just think of the information imbalances that remain no matter what the size of the FDA. The applications for new drug approval are all prepared by scientists that have dozens of years of experience dealing with a single compound for a single treatment. To be sure, cancer becomes a broad umbrella under which many different subspecialties develop. The FDA does not have the institutional capability to develop a parallel expertise on the opposite side of the line. Instead it has to work through all-purpose cancer generalists who cannot match the detailed knowledge that the applicant can muster in support of its ap-

125. See Prescription Drug User Fee Amendments of 2007, Pub. L. No. 110-85, 121 Stat. 823, 825-42 (codified as amended at 21 U.S.C.A. §§ 379g-379j (West Supp. 2009)).

126. David A. Kessler & David C. Vladeck, *A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims*, 96 GEO. L.J. 461, 472 (2008); see also INST. OF MED. OF THE NAT'L ACADS., *supra* note 120, at 193 ("There is little dispute that the FDA in general is . . . severely underfunded.").

127. See SUBCOMM. ON SCI. & TECH., FDA SCI. BD., FDA SCIENCE AND MIS-
SION AT RISK 22 (2007).

128. *Id.* at 6.

129. Matthew Borghese, *Obama's Budget Expands FDA's Food, Medicine Safety Funding*, May 12, 2009, ALL HEADLINE NEWS, <http://www.allheadlinenews.com/articles/7015110502> ("Obama's budget will give an additional 19 percent in funding to the FDA's two major projects; protecting America's food supply and ensuring safer medical products.").

plication.¹³⁰ The knowledge differential leads to excessive caution, which translates into more hesitation, more cost, and more delay. No funding increase can alter this knowledge imbalance. The dangers of permititis rest on the simple observation that the current regulatory structure gives too much power to too few individuals. Money alone cannot change this.

In some sense the situation is even worse. The FDA chokehold position in all likelihood *slows down* the dissemination of information about various forms of drug treatment. Recently the FDA floated an idea to allow drug companies to disseminate information about off-label uses that have appeared in peer-reviewed journals,¹³¹ which means virtually all journals. The proposal has predictably been met with resistance from the adherents of the centralized model who think that the FDA should keep as much control over drug information as possible.¹³² This position seems clearly to be wrong, perhaps even perverse. First, the mere fact that reputable journals publish clinical studies on off-label uses shows that an extensive gray market has developed, which is a sign of a dysfunctional regulatory system. Second, the distribution of peer-reviewed studies responds to the reservations about the FDA system of clinical trials. That system runs its clinical trials on limited populations for limited periods of time. The postrelease studies help overcome both inherent limitations because, almost by definition, they involve longer time periods with larger numbers of patients.¹³³

Encouraging circulation of these articles has the added benefit of increasing the availability of *independent* knowledge about drugs. Ironically, the FDA's proposal to allow only the

130. Cf. U.S. Food & Drug Admin., How Drugs are Developed and Approved, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/default.htm> (last visited Oct. 21, 2009) (noting that a team of "physicians, statisticians, chemists, pharmacologists, and other scientists" reviews any new drug application submitted for FDA approval).

131. News Release, U.S. Food & Drug Admin., FDA Proposes Guidance for Dissemination of Information on Unapproved Uses of Medical Products (Feb. 15, 2008), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116859.htm> (recommending that distribution be limited to peer-reviewed journals with editorial boards that have conflict of interest policies); see Anna Wilde Mathews & Avery Johnson, *Boost for Off-Label Drug Use: FDA Would Let Firms Keep Doctors Informed on Unapproved Methods*, WALL ST. J., Feb. 16, 2008, at A3 (reporting on the FDA proposal).

132. See Mathews & Johnson, *supra* note 131.

133. See ABELOFF'S CLINICAL ONCOLOGY, *supra* note 26, at 327–35 (describing several opportunities for physicians and patients to participate in clinical trials and the review process for clinical trials).

drug manufacturers to distribute the information leads to biased information, as companies can choose to selectively release information.¹³⁴ Instead, the FDA should post *all* the information about off-label uses on its websites, thereby offsetting any perceived weaknesses in the alternative sources of information, e.g., the various compendia about off-label uses.¹³⁵ The objective must be the best dissemination of information to help save lives. The FDA cannot guard against the possibility that posting this information will be interpreted as an impermissible implied promotion of an off-label use; it should not try to maintain that empty façade.

We can take the argument one step further. A better option would be to allow companies to promote drugs for established off-label uses, that is, those covered by Medicare or private insurance. This approach would allow companies to effectively market these drugs. For example, the FDA recently allowed Genentech to gain accelerated market approval of Avastin (bevacizumab) for breast cancer, which immediately resulted in an eight-percent increase in the market value of its shares.¹³⁶ In turn, this accelerated market approval allows Genentech to produce for the new uses, which leads to more rapid informa-

134. See Jeanne Lenzer, *Drug Secrets: What the FDA Isn't Telling*, SLATE, Sept. 25, 2005, <http://www.slate.com/id/2126918/> (noting that even if a drug is already on the market for different uses, trade secret concerns may lead drug companies to not divulge results from failed clinical trials that have adverse events).

135. In general, I support the publication of trade secret information needed to evaluate serious health risks. That also seems to be the general principle in *Corn Products Refining Co. v. Eddy*, which stated:

[I]t is too plain for argument that a manufacturer or vendor has no constitutional right to sell goods without giving to the purchaser fair information of what it is that is being sold. The right of a manufacturer to maintain secrecy as to his compounds and processes must be held subject to the right of the State, in the exercise of its police power and in promotion of fair dealing, to require that the nature of the product be fairly set forth.

249 U.S. 427, 431–32 (1919). This rationale clearly applies to drugs that might have harmful effects; however, similar disclosures of trade secrets should not be applied when these risks of adulteration, misbranding, or danger to health are not present. See Richard A. Epstein, *The Constitutional Protection of Trade Secrets Under the Takings Clause*, 71 U. CHI. L. REV. 57, 61–73 (2004) (discussing which risks should be disclosed and why that raises hard questions of implementation).

136. See Andrew Pollack, *Wider Use of Avastin Is Approved*, N.Y. TIMES, Feb. 23, 2008, at C1 (discussing the increase in share values after Avastin's approval); see also Marilyn Chase & Anna Wilde Mathews, *Genentech Clears Hurdle on Cancer Drug Avastin*, WALL ST. J., Feb. 23–24, 2008, at A3 (reporting on Avastin's approval).

tion dissemination than the NCCN can supply. Genentech undoubtedly gained hundreds of millions of dollars from the FDA decision, but the increase in the market value of the firm *understates* the social gain from this FDA decision. The increase in share value does not include the anticipated consumer surplus (subjective value less market price) to users. These numbers are likely to be very large indeed, given the intrinsic value of life *and* the restricted wealth of many patients—which means that no pricing system, however clever, can capture the entire relevant surplus. There are some fortunate consequences to the imperfect correlation between utility and wealth.¹³⁷ For example, AIDS drugs can produce immense benefits to patients far beyond their ability to pay.¹³⁸ So long as the companies can cover their expenses, they will continue to produce these drugs, even if they cannot capture the full amount of the patient surplus in fees.

V. THE FDA DECISIONS ON CANCER DRUGS

The relative theoretical competence of decentralized and centralized systems is borne out by a closer examination of the FDA's decision-making processes. Generally, the power to issue permits gives administrative officials enormous control. In any permit system the individual applicant has the burden to show that the product in question meets all government safety standards.¹³⁹ Conversely, the standard judicial rule is that injunctions against actions that might harm *other persons* should be issued only after a showing of an imminent risk of a serious harm.¹⁴⁰ Thus the permit system gives public officials far greater power than the standard form of injunctive relief.

The power given to the FDA exceeds its ability to discharge its obligations, as all agree that the FDA lacks the resources or expertise needed to evaluate cutting-edge scientific technolo-

137. See Tomas J. Philipson & Anupam B. Jena, *Who Benefits from New Medical Technologies? Estimates of Consumer and Producer Surpluses for HIV/AIDS Drugs*, 9 F. FOR HEALTH ECON. & POL'Y, issue 2, art. 3, at 16 (2006), http://www.bepress.com/thep/biomedical_research/3/ (noting that even with unregulated prices, drug innovators could only capture about five percent of the social surplus through innovation).

138. See *id.* at 1 (noting that, in the aggregate, there is a \$1.33 trillion dollar consumer surplus in the total lifetime value of HIV/AIDS drugs).

139. Cf. Richard A. Epstein, *The Permit Power Meets the Constitution*, 81 IOWA L. REV. 407, 414–19 (1995) (discussing how permit systems currently operate).

140. See *id.* at 414.

gies.¹⁴¹ The FDA's difficulties do not stop with this endemic problem. Two other issues, each illustrated by recent developments in the field, are also noteworthy. These involve, first, the articulation of standards for intelligent judgment, and, second, the risk of influence from powerful political or economic interests.

A. STANDARDS OF JUDGMENT

Drug bans must necessarily draw sharp lines between products allowed into the market and those which are kept off. Any estimation of safety and effectiveness necessarily lies on a two-dimensional continuum, which makes it nigh impossible to impose defensible rulings on when the ban is desirable and when it is not. Any revision of an initial decision is necessarily subject to similar difficulties. Voluntary organizations, which advise but do not ban, do not face this problem. They report all the information, and members choose which course of treatment to follow based on the report and patient preference.¹⁴² Clearly other factors are likely to be involved, but those complexities do not alter this basic conclusion.

A full evaluation of a particular drug leads some physician-patient pairs to use drugs in ways that other physician-patient pairs will not. The variation in uses allows scientists to update their assessment of the overall utility of a particular product. Thereafter, everyone can make timely revisions of their initial decisions. Use will decline when the early findings are bad and will increase when they are good. Additionally, as more data arrives, the protocols and the counterindications will become clearer, allowing for a greater convergence in judgment over time. These decentralized adjustments are less vulnerable to the peculiar preferences (or prejudices) of a single FDA committee, whose members, after all, are chosen by the FDA itself.¹⁴³

141. See SUBCOMM. ON SCI. & TECH., FDA SCI. BD., FDA SCIENCE AND MISSION AT RISK: ESTIMATED RESOURCES REQUIRED FOR IMPLEMENTATION 8–9 (2008), available at http://energycommerce.house.gov/Press_110/022508.ScienceBoardReport.EstimatedResources.pdf (noting that the “FDA lacks information technology (IT) capability and capacity to support monitoring of drug and food safety and is particularly challenged in the regulation of products based upon new science”).

142. See, e.g., Project Inform: Mission Statement, <http://www.projectinform.org/about/mission.shtml> (last visited Oct. 21, 2009) (“Project Inform . . . supports individuals to make informed choices about their HIV health . . .”).

143. See Steve Usdin, *FDA Reviewing Intellectual Bias*, BIOCENTURY, Apr. 20, 2009, at A11.

If the bottleneck created by the FDA's permit power is removed, the product use will increase, revenues will move upward, and more research will take place.

A further danger of centralized systems is that government officials tend to overrely on objective measures, most notably the extension of life, to decide which products to allow into the marketplace. They cannot enter into complex and subtle tradeoffs. Decisions that deal with quality of life are often put on the back burner. The FDA also ignores the variations of patient responses by basing its decision on average responses.¹⁴⁴ This approach tends to deny licensing approvals to products that serve a fraction of the overall population, even if it is of no benefit to the rest. That appears to be the motivation for the FDA's controversial decision to limit the use of Iressa to persons already on the drug.¹⁴⁵

The severity of these regulatory conflicts is revealed by the recent FDA decision to grant, over much opposition, Genentech an accelerated approval to promote and sell Avastin, its drug for breast cancer patients.¹⁴⁶ The FDA advisory committee voted five to four against the use of the drug,¹⁴⁷ and if that recommendation had been followed, the 38,000 or so women eligible for treatment would have been denied all (on-label) use, with an obvious hit on Genentech's share price.¹⁴⁸ As shown, a single vote looms all too large in the regulatory system that faces sharp discontinuities in outcome no matter where or how it sets its decision point. The opposite is true in a decentralized system, where both sides register their best judgment and allow downstream users to decide whether or not to use the

144. See EPSTEIN, *supra* note 19, at 137 ("The FDA deals only in averages, and the averages don't predict the response of any one individual to either drug." (quoting Steven Walker, Letter to the Editor, *Iressa: The Reality vs. the FDA's Version*, WALL ST. J., July 26, 2005, at A25)).

145. See *id.* at 135–38.

146. See Victoria Colliver, *New Option for Breast Cancer Treatment*, S.F. CHRON., Feb. 23, 2008, at A1 (noting that approval was granted in the absence of any other treatment for metastatic breast cancer).

147. See FDA Panel Nixes Avastin for Breast Cancer, <http://www.pharmalot.com/2007/12/fda-panel-nixes-avastin-for-breast-cancer> (Dec. 5, 2007, 16:36 EST) (noting that FDA medical reviewers found that the slower rate of tumor progression did not offset the increase in side effects).

148. See Heather Tomlinson, *The FDA: Feared Throughout the Pharmaceutical Industry*, INDEPENDENT, Aug. 12, 2001, <http://www.independent.co.uk/news/business/news/the-fda-feared-throughout-the-pharmaceutical-industry-665420.html> (discussing the negative impact of an FDA rejection on a drug company's share prices).

treatment. In any decentralized setting, we can predict that a five-to-four vote against the use by a learned committee would on average result in fewer users than a five-to-four vote in favor. The numerical count will provide some information wholly apart from the knowledge of which panel members took which position. But that difference is likely to be small because there is no discontinuity at the fifty percent point.

The problem is still more worrisome, for on the merits no one is really sure who is right. Evidence suggests that using Avastin in conjunction with Taxol, a well-established drug, delayed tumor progression for about 5.5 months longer than the use of Taxol alone—a clear plus.¹⁴⁹ By the same token, Avastin did not prolong life by any significant measure and had a higher rate of adverse side effects than when Taxol was used alone.¹⁵⁰ The FDA's inclination to question the use of Avastin is understandable because the objective measures do not stack up well in comparison trials. But so what? One reason why the principles of full disclosure and informed consent have gained such traction is that they respect subjective preferences on questions concerning the quality of life.¹⁵¹ Within a decentralized system, the downward push of information allows potential users to absorb it seamlessly. If physicians are “split” over the use of a drug such as Avastin, then patients' decisions will likely follow that division. An administrative decision that converts a five-to-four vote against a drug into a legal regime that prohibits its use is illogical in close cases. And, again, note this abiding asymmetry: a vote of five to four in favor does not require all to use the drug, but allows all patients to choose to use it. The distribution and interpretation of information strongly favor a decentralized system that relies on persuasion.

B. EXTERNAL INFLUENCES

The process to decide whether the FDA should approve a drug does not take place in hermetic environment in which the science, and only the science, governs the ultimate outcome. By necessity there are always political overtones that arise because of the identity of the permit applicant and its potential customers and competitors, all of whom have some access to the

149. See Pollack, *supra* note 136 (reporting that women went a median of 11.3 months before their cancer worsened or they died when they used Avastin in combination with Taxol, compared with 5.8 months if they just took Taxol).

150. See *id.*

151. See Schuck, *supra* note 29, at 924–25.

FDA and to the congressional committees that oversee its actions. Competitors, for example, stand to lose market share if a rival product is licensed for sale. The FDA is subject to constant political pressure, such as the nonstop, bipartisan attacks of influential figures Senator Charles Grassley and Representative John Dingell, on the ineffective protection that the FDA renders to consumers.¹⁵² Other political actors are reluctant to attack Senator Grassley, whose support might be needed on other health care issues such as Medicare reform.¹⁵³

On the economic side the stakes are also enormous. If a second drug in a given class enters the market then it undercuts the monopoly obtained by the first to enter. Even in a duopoly situation, unit prices often fall by thirty percent or more in markets where sales could amount of tens, even hundreds, of millions of dollars per year.¹⁵⁴ Therefore, competitors often take steps to torpedo their rivals' FDA applications. One recent example involves the FDA decision to delay approval, for more tests of course, of the cancer vaccine Provenge, which had shown promising results on certain classes of prostate cancers.¹⁵⁵ The FDA decision was roundly attacked in thousands of letters by angry persons who thought that this vaccine held out some hope for patients.¹⁵⁶ The account of the matter published in *Nature Biotechnology* stated that approval delays for Provenge went against the advice of an advisory committee.¹⁵⁷ The

152. See, e.g., Alicia Mundy, *Dingell, Grassley Call for Overhaul of Agency 'Culture'*, WALL ST. J., July 30, 2008, at A4 (reporting that reforms proposed by Senator Grassley and Representative Dingell, aimed at increasing the FDA's effectiveness, would give the FDA the power to levy fines, expanded power to order drug recalls, and the authority to impose additional limitations on drug advertisements); see also Press Release, Charles E. Grassley, Ranking Member, U.S. Senate Comm. on Fin., Grassley Asks for an Accounting of Contacts Between FDA and Device Maker (Mar. 6, 2009), available at <http://finance.senate.gov/press/Gpress/2009/prg030609d.pdf> (noting what Grassley deems "a 'too cozy relationship' between the FDA and industry").

153. See Usdin, *supra* note 108, at A2.

154. LUIS M. B. CABRAL, INTRODUCTION TO INDUSTRIAL ORGANIZATION 112 (2000) (noting that duopoly prices are lower than monopoly prices).

155. See Editorial, *The Regulator Disapproves*, NATURE BIOTECH., Jan. 2008, at 1, 1 (discussing the FDA's decision to delay approval of the cancer vaccine Provenge, calling it a "knee-jerk defensive response to accusations of process impropriety").

156. See *id.*

157. See *id.* Advisory committees are composed of experts in a given field to advise the FDA on whether and how to approve certain types of drugs. See U.S. Food & Drug Admin., Advisory Committees, <http://www.fda.gov/AdvisoryCommittees/default.htm> (last visited Oct. 21, 2009) (discussing the composition of FDA advisory committees).

report further stated that Provenge's denial was triggered by a critical letter from Howard Scher, a doctor in the Memorial Sloan-Kettering Cancer Center, who had an undisclosed financial and fiduciary interest in a rival drug Asentar.¹⁵⁸

Conflict of interest regulations require routine disclosure of these connections, thereby allowing public authorities to discount these claims, if they so choose. Nonetheless questions of undue influence still remain. Unfortunately, permititis makes the entire information system more vulnerable to subversion than the NCCN and similar voluntary organizations, where a few powerful individuals or institutions are not in a position to subvert new or experimental drugs. Improper evidence could, of course, mislead NCCN members. Any potential harm is cabined because voluntary organizations cannot issue bans and other information can surface to counteract previously misleading facts. Yet this key fact remains: the redundancy of a decentralized information system offsets its failings and makes it resistant to political maneuvers that are inherent when government officials exercise the permit power.

CONCLUSION

This article is a conscious outlier from other treatments on the vexed topic of FDA power. In it, I do not ask *how* the FDA should exercise its permit powers; instead I focus on the prior question of *whether* the FDA should have those powers at all. My analysis is not meant to be ad hoc or personal. Rather, it starts from a general political theory which maintains a strong presumption against the use of the permit power to regulate autonomous individuals. It then examines FDA activities to identify some sufficient reason to overcome that presumption. The search is futile. The standard justification for the use of state power, namely the protection against the risk of force or fraud, plays little if any role.

Nor does it appear that the FDA can engage in some well-calibrated campaign of consumer protection against the hasty and unwise choices that people undoubtedly make in their own lives. To be sure, it would be foolish to dismiss this risk on the ground that all individuals are imbued with a natural talent to make only rational choices. They aren't. But it takes more than this showing to justify the FDA's expansive permit power. First, the mode of distribution of drugs matters. Greater con-

158. See *The Regulator Disapproves*, *supra* note 155, at 1.

cern exists about impulsive, habitual, or otherwise foolish behavior when individuals have direct access to certain drugs. Here we should be highly cautious about bans, even while entertaining the possibility. Cancer drugs are always distributed through professional intermediaries with ready access to scientific and technical information. These intermediate organizations play an extensive role right now, even as the FDA exercises its strong gatekeeper function. Allowing one on-label use does not decide whether a drug should be used, or whether that use should be alone or in conjunction with other drugs. It does not decide whether that drug should be used as a first-line or second-line treatment. Nor does it even hint at the structure of the gray market culture of off-label uses.

The key conclusion is that voluntary current mechanisms for both on-label and off-label uses are far more likely to work across the board. In this arena, two systems of control are *not* better than one. Rather, public investments in the FDA's permit power will likely yield a negative return. Decentralized bodies are more likely to make sounder decisions. As information is collated and presented, slow shifts in uses and behaviors under a legal regime that facilitates continuous updating and experimentation should be expected. Even if the FDA obtains additional resources, it could not discharge its chosen mission. At any resource level, the FDA is a second-best relative to the current private systems and these systems could be improved further if drug companies were allowed to participate in the dissemination of information generated by independent sources. Right now, the prospects for incremental FDA reforms are unlikely. No matter how Congress tinkers with the present framework, the FDA would still use control over the processes that systematically underestimate the risks of delay, would ignore variation across individual cases, and would be vulnerable to enormous political and economic pressures. The FDA's permit power is an open wound in the body politic. Permititis cannot be controlled; it should be eliminated.