

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

**By**

**Richard A. Epstein\***

**A Modest Thesis: Remove FDA Control over Cancer Drugs** The central theme of this conference deals with the proper scope for the FDA in the regulation of cancer drugs. 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. But I do have some knowledge of questions regarding the institutional arrangements in which these choices should be made. In examining this issue, I start from a classical liberal presumption that government intervention is to be treated as a bad until it is shown to be a good. To put the proposition in quasi-medical terms, permittitis—the ability of government agencies to block voluntary personal decisions, should be regarded as a danger to be avoided rather than as a progressive development worthy of social support backed by public funds.

This presumption against the use of the permit power applies across the board to all forms of government activity, including those which relate to the health and safety of the public at large. The reason why a heavy burden ought to be placed on government use of the permit power is that this power allows administrative agencies to exercise monopoly power over the lives of ordinary citizens without their consent. In so doing it seeks to substitute its judgment for their judgment on matters of direct and vital concern to them. To justify the assertion of government power, the state must show at a minimum that the decisions it makes for other people are better than the decisions that they are able to make for themselves by an amount that offsets the loss of liberty—an intangible but important value—and the administrative costs of the system. That burden is sometimes carried when the government seeks to control activities that hold out the risk of harm to others. Although even in this context, there is a regrettable tendency to ban activities (as

---

\* James Parker Hall Distinguished Service Professor of Law, The University of Chicago; the Peter and Kirsten Senior Fellow, The Hoover Institution; Visiting Professor NYU Law School. I should like to thank Dr. Brian Durie of UCLA Medical Center for his helpful explanation of the NCCN. Needless to say, all conclusions on the role of the FDA are mine alone.

by delaying nuclear power plants, for example) long before they manifest any harms. But the FDA's jurisdiction does not involve harm to strangers, only potential harms that individuals may, or may not, inflict on themselves. In this context, the case for the ban faces a still higher burden of proof.

Within the context of the FDA, any ultimate judgment necessarily depends on the sources of error in both public and private decisionmaking. In working through this analysis, it is critical to select the right source of comparison, which does not look at the knowledge of the government agents relative to that of the individual patient, or even the individual patient acting under the advice of a professional physician. Oftentimes, the key to any assessment of relative institutional competence is asking how various private voluntary organizations—typically in the nonprofit sector—are able to collect and organize information in ways that improve the caliber of decision made by individual physicians and patients. In so doing, it is necessary to ask the question of whether a rigid state system of permit and certification can outperform a decentralized system that has all the incentives to speed accurate information about cancer therapies to the intended users. I do not think that this burden can be met. The critique here is not directed to particular individuals inside the FDA, but to the basic incentive structures that define its role as a comprehensive regulator. No grant of monopoly power is justified if private institutions are able to provide better information at lower costs than the state.

In order to make out this case, I proceed in steps. Part I deals with the question of how to properly analyze the two kinds of errors that arise in any context that requires decisionmaking under conditions of uncertainty. Toward this end, it deals first with the question of the costs that should be minimized, and argues that in any rational choice environment that figure should be the sum of errors from over and undertreatment, wholly without regard to whether the harm in question is caused by a therapeutic agent or a natural cause. Part II then argues that any error analysis will require all persons, whether as regulators, physicians, or patients to obtain reliable information to minimize the costs of error by, in effect, the same imperfect cost-benefit techniques. Part III follows up by asking whether any private system of malpractice actions could play an effective role in policing physician, hospital, and manufacturer behavior in making these judgments, and concludes that these private rights of action have, and should have, little

or no role to play in the distribution of new cancer therapies. With private rights of action put off to one side, Part IV the examines the relative case for coercive and private action, and concludes that while state coercion is necessary for dealing with matters of adulteration and counterfeiting, in cancer cases, it has little role to play in dealing with the processing of information that can be done better and more cheaply by private parties who use persuasion not coercion to disseminate information. Part V then examines the underlying pattern of centralized control within the FDA, and concludes that it works no better in medicine than anywhere else. Part VI finishes with an examination of two major difficulties of the FDA's centralized processes, namely, their inability to make continuous decisions, and their vulnerability with respect to political and economic influences. A brief conclusion follows.

**I. Causation and Cost/Benefit Analysis** Most of the papers presented will examine the internal FDA procedures in dealing with applications for cancer drugs. The likely framework of analysis asks how its administrative decisions can minimize the two forms of error associated with any dangerous drug or therapy. Type I error, or a false positive, arises when one approves a drug that causes net harm and type II error, or a false negative, arises from what might be termed its improper nonuse, namely, the decision by regulators to keep drugs off the market that have a positive expected value in use for at least some identifiable set of patients. This familiar statistical tradeoff is not distinctive to the FDA's role in evaluating cancer drugs. The same calculations have to be made constantly in other areas, such as environmental and urban policy. Nor within the cancer area is the FDA the sole party that makes these calculations. For approved drugs, all physicians and patients have to decide collaboratively whether or not to embark on a particular course of chemotherapy, whether for an on-label or off-label use. In so doing, they typically engage in a personalized cost/benefit analysis of the various courses of action.

In both regulatory and personal decisionmaking settings, there is one key trap to avoid—that is, drawing a philosophical, moral, or functional distinction between the harm that is caused by the treatment and that which is caused by the disease. That distinction is often made in a wide variety medical contexts, including discussions of euthanasia, because we can in fact identify many other legal contexts in which the

difference between harm caused by a natural event and harm caused by a particular human agent matters greatly. Thus the early development of the tort law governing liability in personal injury and death cases concentrated on cases, referred to above, where the actions of one person caused harm to a stranger, either by intention or by inadvertence.<sup>1</sup> Hitting other individuals or creating dangerous latent conditions are the paradigmatic illustrations of these cases. In these settings it still matters whether, for example, the boulder that landed on the plaintiff was set in motion by natural forces or by the actions of a human being. On the one side, it is difficult to impose a duty on any one individual to guard against the natural misfortunes that befall another. And, on the other, holding someone responsible for the damages inflicted on a stranger makes good sense when that person does not benefit in any way, shape, or form, by the defendant's conduct.

That approach used in stranger case is wholly inapplicable in any and all treatment settings, where the parties do not stand as strangers to each other, but as persons joined together in a cooperative arrangement. Now one potent reason to encourage the *deliberate* infliction of harm is the expectation that this *aggressive* response (note the ambiguity in the word "aggressive") will relieve a greater harm to which the treated person has, or soon will, fall prey. Now the benefit side of the equation counts because the operative assumption is that parties enter into particular voluntary interactions, including those for the provision of health care, with the expectation of mutual benefit. To isolate the planned harms for rebuke, without considering their associated benefits, is to deny the rationality of the whole decisionmaking procedure. People enter into a course of treatment, for which they pay hard dollars, *not* to minimize the risk of Type I error in which they are killed or hurt by drug therapy. They wish to minimize the *sum* of errors no matter whether caused by either natural events or by human intervention.

---

<sup>1</sup> See, for my general statements on this point, Richard A. Epstein, *Medical Malpractice: The Case for Contract*, 1 *Amer. Bar Found. Res. Journal* 87 (1976); Richard A. Epstein, *The Path to the T.J. Hooper: Of Custom and Due Care*, 21 *J. Legal Stud.* 1 (1992). The distinction is found in many, but by no means all, cases. See, e.g., *Pfaffenbach v. White Plains Express Corp.*, 216 N.E.2d 324 (N.Y. 266 1966); *Holland v. Pitocchelli*, 13 N.E.2d 390 (Mass. 1938), for modern applications, and *Farwell v. Boston & Worcester R.R. Corp.*, 45 *Mass.* 49 (1842) for its historical use.

The failure to identify the proper maximand has led to serious distortions in health care policy generally. One central precept of medical ethics—which is honored as much in the breach as the observance—relates to the sovereign power of choice that each individual has to refuse various forms of medical treatment.<sup>2</sup> No physician, no government no matter how wise can force any competent individual, however foolish, to accept treatment against his or her will.<sup>3</sup> The notion of self-rule and governance is allowed in large measure on the ground that no individual should be required to take the risk, or suffer the harm, associated with the administration of medical treatment. These decisions to refuse are personal. Individuals may, and usually do, seek advice from 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 rather from the commonsense observation that people have the right incentives to deal with their own health issues and therefore will devote more attention to these decisions when they cannot be second-guessed. There are of course protections against fraud and undue influence that have to be introduced, but these are not done in the form of preclearance devices. Rather, individual lawsuits can be brought in particular cases against those parties who engage in improper conduct.

In modern health care settings, however, the principle of autonomy always comes off second best when the question turns to the right of any individual to *accept* medical treatment that could cause harm, alleviate suffering, or both. At this point the language of autonomous choice is often invoked, but the subtext is different. Some agency or board should be put in the position to protect autonomous individuals of limited ability

---

<sup>2</sup> For my recent discussions of this issue, see Richard A. Epstein, *The Erosion of Individual Autonomy in Medical Decisionmaking: Of the FDA and IRBS*, 96 *Geo. L.J.* 559 (2008) [hereinafter, Epstein *Erosion of Individual Autonomy*]; Richard A. Epstein, *Defanging IRBs: Replacing Coercion with Information*, 101 *Nw. L. Rev.* 735 (2007) [Epstein, *Defanging*].

<sup>3</sup> “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.” *Schloendorff v. Society of New York Hospital*, 105 N.E. 92, 93 (N.Y. 1914).

from making their own choices, lest they make too many mistakes.<sup>4</sup> The legal approach slides imperceptibly but inexorably from self-determination to paternalism.

The sound approach to patient autonomy is, however, inconsistent with any effort to distinguish the right to receive drug treatment from the right to refuse it. To raise the ante for drug approval or use on the ground that it is “worse” in this context to kill than to let die is, therefore, at cross purposes with the basic rationale of health care. The individual patient is trying to minimize the sum of two kinds of error, and will adopt any strategy where the expected outcomes in all states of the world yield a gain that is greater than the cost of treatment. It is critical to note, however, that the incentives of the FDA or any other regulator do not align themselves properly with these expected value calculations. All agencies are subject to political pressures, and these are most likely to arise in cases where their actions cause *visible* harms that can be traced back to their decisions. The harms that are caused by particular therapeutic agents—e.g. thalidomide—will attract immense attention and give rise to political pressures to take active steps to ban such dangerous products from the marketplace. There is, in effect, 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 about letting new therapies on the market than the FDA. They represent individuals who regard the loss of medical treatment as a real and not a hypothetical risk. Their efforts resulted in a spirited but unsuccessful constitutional effort to pry out from the FDA grasp the right of any individual patient to use any drug that has passed stage I clinical trials. That proposal met an initial round of success in the District of Columbia Circuit Court that took the autonomy question seriously, but it was ultimately and decisively dashed by in an en banc hearing. There it was held FDA authority over health

---

<sup>4</sup> That progression is evident in the Belmont Report. See The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (1979). For criticism of its “weak and distorted understanding of self-determination,” see, Larry R. Churchill, *Toward a More Robust Autonomy*, in *Belmont Revisited* 111 (James Childress et al. eds., 2005). For my own proposal to convert from their current function of gatekeepers to information assemblers, see Richard A. Epstein, *Defanging*, *supra* at .

matters was wholly consistent with our 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.”<sup>5</sup>

Anyone concerned with the policy dimensions of this dispute should not treat that judicial victory as a vindication of the soundness of their substantive views. The real question here is not collective choice through legislation, but individual choice on matters of unique personal decision. The constitutional attack in *Abigail Alliance* is meant to exclude legislative dominance from an area where it does not belong and, in that sense, is no different from cases in which people have rightly defined marital and individual privacy on matters of sexual behavior. Any judicial decision that praises deference to legislative behavior simply sidesteps the serious questions of whether legislative intervention in these personal precincts is justified as a matter of right.

The hard question remains whether in principle there is any reason to believe that state intervention, normally a bad, becomes in this instance a good. To be sure, the entire process here involves delicate questions of valuation of different states of disease and discomfort, and hard judgments on the probability of different outcomes. But that true proposition does not tip the balance back toward an FDA-approval system. Pointing out the practical problems in making rational choices does not undermine the proposition that harms caused by a therapeutic agent should be weighed no more, and no less, than those caused by the natural condition that the treatment is intended to counteract. If we accept, as we must, that individual patients, in consultation with their physicians, have to make a raft of key decisions about the course of treatment when multiple approved therapies are available, the root question is this: if they 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 objection frequently made is that desperate patients could be swayed by false optimism or bad information. Yet that point invites two responses. The first is that the identical risks arise when individual physicians and patients are forced, as they always

---

<sup>5</sup> *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, 445 F.3d 470 (D.C. 2006), *rev'd en banc*, 495 F.3d 695, 713 (D.C. Cir. en banc 2007). For my discussion, see Epstein, *Erosion of Autonomy*, at 574-576.

are, to make choices among lawful therapies. Do victims of prostate cancer prefer radiation, surgery, chemotherapy or pellets, or some combination thereof? Yet no one concludes that in this and thousands of similar contexts the power of choice should be withdrawn from individual patients because of the distinct possibility of its erroneous exercise. The usual response is to counsel prudence in making private decisions or, more dubiously, to impose procedural hurdles—you must have counseling—before making them. But it is not to ban them. The second response is that the information gaps that give rise to the risk of error and fraud also invite strong institutional responses to minimize those risks. But once again it is a mistake to throw out the baby with the bathwater and to assume that the imperfections in individual choice require some collective decision to let certain drugs on the market before used. Again, some 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, as noted, of special importance in cancer cases, where the stakes are large and the costs of error are high. Time is of the essence in responding to tumor growth; the earlier the detection, the more likely the prospects of successful treatment. Exactly what counts as a successful treatment is a subject to which I shall turn, but for the moment it is best to bracket that question. At the same time, the high toxicity of many cancer treatment agents means that the use of the wrong compound or drug could lead to either serious discomfort, earlier death, or both, for the treated patients. The right frame of mind therefore makes it clear that the upside from proper treatment is likely to be low in the sense that cure is often not a possibility, and the best hope is to prolong life by years, or even months, perhaps, but not necessarily at an improved quality of life. The insistence that all acceptable cancer drugs supply a complete cure is likely to make the best the enemy of the good, all in the search for unattainable perfection. Rather, the usual protocols call for the use of multiple drugs in sequence, starting with the least toxic first-line treatment, and slowly working up the chain to riskier or less tried options as the choices narrow. Where a treatment starts to falter, the next, and stronger, agent is used in turn until the drug cabinet is empty.

We thus have this grim scenario for any/cost benefit analysis that is neither eliminated nor introduced by regulation. Cancer patients are precariously perched on the unhappy horns of an inescapable dilemma. The costs of inaction are high, often death. The costs of action are high, often a faster death or serious distress. But treatment has an upside which could, but need not, justify the result. The necessary decisions involve high rates of error in both directions, where each error carries a high expected loss. Yet however grim the prospects, the same methodology applies: maximize expected value in treatment vel non, such that one defensible option is hospice care without treatment when all the alternatives look worse. In these varying situations, *reliable information really matters*, for the one strategy that makes little sense is to base decisions solely on the casual accretion of information. Put otherwise, a small reduction in the probability of an adverse outcome or short remission from treatment could amount to enormous value.

Here is a simple explanation why. One general conceit on valuation holds that all human beings should, bionically speaking, be treated as \$6 million men and women.<sup>6</sup> 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 5 percent and, as a first approximation, there is substantial social gain, which if not \$300,000 is still substantial. With error costs high and mistakes common, it makes sense for everyone to invest heavily in knowledge. Stated more formally, the question is always whether the improvement in outcomes for the individual (and through that person, for society, as there are no real conflicts here) is greater than the costs of obtaining the better information. With most naïve patients, the answer is so clearly yes in both regulated and unregulated markets that no cancer patient relies on his or her own judgment to decide which course of therapy or nontherapy to follow. Instead, at each point in time the operative inquiry should be, and often is, whether a further investment in information costs less than the gain from any anticipated reduction in error costs. In many cases this

---

<sup>6</sup> See Kevin Murphy & Robert Topel, Diminishing returns? The costs and benefits of improving health, 46 *Persp. Biol & Med.* S108 (2003). There are many complications here, including questions of the sensitivity of the value of life to age and health conditions. But the revealed behavior suggests a high number.

turns out to be the case, and so we have the question of how to organize our systems of social control to maximize the rate of return from investments in additional units of information.

**III. The Irrelevance of Tort Liability to Cancer Cases** The problem of information assembly is in no sense distinctive to cancer treatment (although it is severe in these contexts). It is therefore appropriately governed by the general law applicable to physicians, hospitals, drug, and device companies, much of which is designed to secure the production and sensible use of this information. The rise of informed consent in the 1960s and 1970s, for example, represents an effort to harness that information by obligating the doctor in routine cases to disclose to patients the risks (both by probability and severity) associated with the ordinary provision of medical care.<sup>7</sup> Nuances of doctrine, however, are not the key concern. Any sensible approach worries less about whether the initiative lies with the patient or the physician. The major objective is to encourage actively all parties to take cooperative steps so that the patient learns about treatment options while the physician learns about the patient's lifestyle preferences. Similarly, within the framework of the drugs the key question, often tied up with the so-called duty to warn, is first to transmit within the profession information about the generalized costs and benefits of certain costs of treatment, which can thereafter be mapped on to patient preferences. Both sets of interactions are sure to take place even if the law placed no duty to warn or disclose on physicians, hospitals, or drug or device manufacturers. The information is just too valuable, so that people will seek it out actively whether the patient must ask for information or the health care provider is duty bound to supply it.

Once, however, legal rights and duties enter into the equation, which system of controls should be adopted to insure the orderly flow of information? In some situations, a credible case could be made for using common law tort actions against health care providers that do not supply or rely on proper information. Suits for the failure to obtain "informed consent" are the most obvious illustration of this approach. In general, however, the prospects of these actions have diminished over time. Unlike 35 years ago,

---

<sup>7</sup> See, e.g., *Canterbury v. Spence*, 464 F.2d 772 (D.C. 1972).

today's physician is no longer the only source of information about the potential pitfalls and advantages of certain treatment. Online sources are too ubiquitous to ignore. In addition, physicians and hospitals have become proactive in this area, partly out of a fear of litigation, and partly out of the correct sense that strong patient (and family) participation helps promote favorable medical outcomes. In practice, today, suits based solely on want of informed consent are hard sells for plaintiffs.

The legal position is more complicated in suits against the suppliers of various drugs and medical devices, where the legal system holds product suppliers responsible for failure to provide adequate information about their products, including perhaps warnings beyond those required by the FDA. The case law on this topic is enormous, and there are heavy overtones of FDA involvement. The earlier position of the FDA was that it was quite content to see state courts develop tort remedies even for companies that supplied FDA-required warnings.<sup>8</sup> The more recent FDA position has been to oppose state law efforts to impose additional warnings in drug cases including, of course, cancer drugs.<sup>9</sup> That legal position is complicated because the FDA has in place specific procedures to allow for updating of warnings of adverse events. Although these are infrequently used<sup>10</sup> they do make it harder to maintain that the current law prohibits companies from updating their warnings.

The details of current law should not detain us here. What matters is basic policy. I have favored strong preemption as a matter of principle. Needless to say, that position has been frequently attacked. Recently, David Kessler and David Vladeck have stoutly defended the use of the tort system to offset the underperformance by the FDA.<sup>11</sup> I think

---

<sup>8</sup> See, e.g., *MacDonald v. Ortho Pharmaceutical Corp.*, 475 N.E.2d 65, 70 (Mass. 1985).

<sup>9</sup> See, e.g., *Horn v. Thoratec Corp.* 376 F.3d 163, 169 (3rd Cir. 2004).

<sup>10</sup> See, 212 C.F.R. § 314.70c (2006), noting the possibility “to add or strengthen a contraindication, warning, precaution, or adverse reaction.” For discussion, see 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, 470-475 (2008) (noting the limited FDA resources to monitor the marketplace).

<sup>11</sup> *Id.* at 491-95 (2008).

that this approach is wrong for two reasons as a matter of general principle.<sup>12</sup> First, it understates the high error rates that accompany private rights of action. The tort system is too complex, and the factual evidence too uncertain, to make the tort system a reliable corrective of any FDA error. Second, and more importantly, the private right of action at best works only in cases of inadequate FDA monitoring. Unfortunately, it cannot undo, and can only compound, the errors of excessive FDA overenforcement. The remedy has to be made available in all cases and not in none, and the constant insistence that the FDA sets only “minimum standards,” while widely repeated, ignores the high level of variation in FDA practices.

In cancer cases, however, the detailed rules of the tort system do not much matter. Here medical malpractice and product liability suits are at most bit players. No cancer patient makes an attractive plaintiff for two reasons that no lawyering can overcome. The plaintiffs are usually old and they are always sick, commonly with short life expectancies. Those two facts necessarily prevent even an astute plaintiff’s lawyer from collecting damages under any of the three standard heads of liability for damages: pain and suffering, lost income, and medical expenses.<sup>13</sup> To be sure, the wrong treatment in cancer will produce pain and suffering. Yet the same is true of the right treatments, which are also known for their toxic side effects. So long as *incremental* pain and suffering is the appropriate measure of recovery in a tort case, these damages will be minimal at best. Lost earnings usually do not count as an element of recovery because the patient condition precludes further gainful employment no matter what course of action is followed. And medical treatment is expensive—perhaps more so—if the right course of treatment is followed. With damages small in all its relevant dimensions, few lawyers are willing to risk the certainty of heavy expenses for the uncertain prospects of a limited recovery in trying circumstances where much deference is given to both the physicians

---

<sup>12</sup> Richard A. Epstein, *Why the FDA Must Preempt Tort Litigation: A Critique of Chevron Deference and a Response to Richard Nagareda*, 1 J. Tort Law, (Article 5), (2006), for Professor Nagareda’s intriguing proposal to see the lure of FDA preemption to encourage drug companies to engage in post-marketing surveillance, see Richard A. Nagareda, *FDA Preemption: When Tort Law Meets the Administrative State*, 1 J. Tort Law, (Article 4) (2006).

<sup>13</sup> For a discussion, see Richard A. Epstein, *Torts*.

and suppliers of goods. The only cancer cases with favorable prospects are those that have little or nothing to do with the course of chemotherapy. One example is where the plaintiff claims that a physician's missed diagnosis cost him or her the chance of a successful cure.<sup>14</sup> Another situation involves patients who suffer collateral damage when their cancer is in fact cured.<sup>15</sup> No longer is the suit a direct challenge to medical judgment in difficult circumstances. Now it rests on the more modest and more persuasive claim that simple precautions applicable to routine surgeries would have avoided serious illness entirely, so that large damages for pain and suffering, lost income and medical expenses are now appropriate. Few cancer cases have this profile.

Similarly, serious cancer cases raise no issues of consumer protection or overpromotion that have been brought against painkillers like Vioxx<sup>16</sup> and statins like Lipitor.<sup>17</sup> No oncology treatments are sold over the counter, and none are advertised to the public at large. All cancer drugs (and other forms of cancer treatment) are necessarily routed through physicians and hospitals, all of whom have professional and institutional expertise. There is therefore little prospect that tort litigation will impact on the use of

---

<sup>14</sup> See, e.g., *Herskovits v. Group Health Cooperative*, 664 P.2d 474 (Wash. 1983). It should hardly inspire confidence that the court did not make the correct calculations on how to determine the incremental gain to a patient whose chance of recovery fell from 39 to 25 percent because of a missed diagnosis. The issue of whether the delayed diagnosis was more likely than not the cause of death was equal to 14/75, or slightly less than 20 percent, which was the one ratio that never made it into the opinion.

<sup>15</sup> See, e.g., *Keir v. U.S.*, 853 F.2d 398 (6th Cir 1988). Plaintiff's eye cancer was cured, but she was left with 20/300 vision and a detached retina. The physician's negligence constituted "failing to perform a dilated examination with an indirect ophthalmoscope." See also *Boyce v. U.S.*, 942 F. Supp. 1220 (E.D. Mo. 1996), holding that amputation of an arm was a violation of the applicable standard when used to treat cancer.

<sup>16</sup> The key litigation here involves claims for recovery of money paid over for the use of drugs that *worked* on the ground that cheaper alternatives would have been adopted if the truth had been fully told. For the progression, see, *Desiano v. Warner-Lambert Co.*, 326 F.3d 339 (2 Cir. 2003), plus subsequent remand cases before Kaplan, J.

<sup>17</sup> For the risks involved, see the recent Pfizer announcement pulling the ads for Lipitor that showed a Dr. Jarvik look-alike rowing a boat. Release of February 25, 2008, Pfizer Voluntarily Withdraws Lipitor Advertising Featuring Dr. Robert Jarvik: Company Commits to Ensuring Greater Clarity Regarding Spokespeople.

cancer drug treatment. Any dissatisfaction with the treatment can be addressed solely through the system of administrative regulation that governs the introduction and use of new cancer drugs. The remainder of this paper is therefore directed to the question of whether, and if so how, these drugs should be used, which depends heavily on the evaluation of their expected costs and benefits. Once again information lies at the core of the story.

**IV. Government Monopoly Versus Voluntary Intermediaries** Once systems of tort liability are put to one side, what forms of regulation help secure the prompt and accurate dissemination of information about cancer drugs? This problem is not, of course, unique to cancer therapy, for it necessarily arises in any context that places a high premium on the dissemination of new and accurate information. The central question is how government or voluntary institutions, or both, may be used to overcome any information shortfalls. The right answer, I have come to believe, is that the government through the FDA should step out of the approval and permit process, and allow the entire matter to rest in the hands of physicians and their patients (hence my title “Against Permittitis”) on the ground that the supposed cure is worse than the underlying disease.

In making this judgment, I am not claiming that the FDA has no role to play in the protection of public health, even if it should have no role in the approval or disapproval of cancer therapies. A powerful state presence is needed, for example, in order to insure the health and safety of the public at large. The FDA needs more focus and more resources to deal with the rash of contaminated foodstuffs that have poured in from overseas—think China—and with the extensive and resourceful counterfeiting and piracy rings that seek to inject defective foods and drugs into this nation’s distribution pipeline.<sup>18</sup> Honest manufacturers of course will go to enormous length to protect their brands against erosion through defects in quality, as Johnson & Johnson did in recalling Tylenol when some unknown person laced its tablets with cyanide.<sup>19</sup> Yet these private

---

<sup>18</sup> Find WSJ story or editorial that notes the private responses of avoiding these countries for getting information

<sup>19</sup> mallenbaker.net, Companies in Crisis - What to do when it all goes wrong Johnson & Johnson and Tylenol, <http://www.mallenbaker.net/csr/CSRfiles/crisis02.html>, recounting the steps taken in response to 1982 and 1986 incident when seven persons

efforts must be backed by state power that can impose criminal sanctions on various malefactors who try to pass off of dangerous or purloined goods. Indeed, in many situations, private parties welcome and advertise “FDA-approval” in order to increase the level of consumer confidence.

The types of questions involved with oncology, however, have little or nothing to do with matters of purity or consumer confidence. In particular, there is no need to strengthen public communication, which is critical for dealing with drugs such as the diabetes medicine Avandia, that are taken regularly by large numbers of ordinary individuals.<sup>20</sup> Oncology drugs are distributed only through channels that reach people who understand why they are being administered. In cancer cases, the task is to assemble information that picks up on the endless tradeoffs between the safety and effectiveness of given drugs. For this task, it is too dangerous to give *any* individual or group, however skilled or competent, monopoly control over whether other people may use a particular good or service. Let the state agency make a negative decision and the product or service may not be sold at all, which carries with it very high error costs. Even if the FDA allows the drug to be marketed, it can subject it to various conditions that relate to pricing, advertising, permissible users, and the like which can limit the dissemination or use of the drug. With complex and dangerous products, these mandatory warnings, instructions, and attached conditions can present formidable obstacles to product marketing and hence product use. Warnings that stress negative side effects are calculated to lower estimations that potential users may make of the expected gains from product uses. Additional procedures and delays can simultaneously raise costs, leading many people who are likely to benefit from certain treatments to forego their use; this has happened with Prozac where the drop in use for treating depression in teenagers and

---

died in Chicago of Tylenol that had been laced with cyanide. Losses of market value of one billion in stock prices in the first instance spurred the creation of tamper proof packages and wide recalls.

<sup>20</sup> Peter Pitts Embed with the FDA, [http://drugwonks.com/2008/02/embed\\_with\\_the\\_fda.html](http://drugwonks.com/2008/02/embed_with_the_fda.html), February 28, 2008 (noting erosion of consumer trust in the FDA).

young adults is highly correlated with increases in the suicidal behavior that Prozac has been said to cause.<sup>21</sup>

If a state monopoly is ineffective, then what could be? One implicit but incorrect assumption in this debate is that FDA competence has to be compared with the knowledge of the individual physician and patient, both of which could prove quite limited. Defenders of the FDA are right to point out that collective generation of the information is likely to be superior to individual impressions. But they are wrong to assume that only government agencies with monopoly powers can assemble and interpret the relevant information. Given the value of this information, the right comparison to the FDA are the voluntary associations, including those for dealing with oncology and other medical specialties<sup>22</sup>, that *right now* serve as responsible intermediaries between the individual patients and physicians and the manufacturers or sellers of cancer drugs.

These intermediate voluntary organizations are not some whimsical creations that are here today and gone tomorrow. Their use is a fixture in a huge range of contexts that have nothing to do with cancer or medicine. These voluntary associations are typically nonprofit, and their basic function is the same in virtually all markets. Once market participants recognize the information shortfall, these voluntary groups funnel, digest and

---

21 See Robert D Gibbons, et al., Early Evidence on the Effects of Regulators' Suicidality Warnings on SSRI Prescriptions and Suicide in Children and Adolescents , 64 Am J Psychiatry 1356-1363 (September 2007): The abstract states the conclusion as follows: "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."

22 See, e.g., CTS NET: The Cardiothoracic Surgery Network, <http://www.ctsnet.org/>, one of whose entries reads: STS Expands the Scope of the National Database, distributed by blast email. <http://www.ctsnet.org/announcements/announcement705.html>. "The rationale for the incorporation of these Identifier Fields into the Database is to enhance its ability to function as a tool for longitudinal follow-up of patients, and specifically, to enable the Database to track the long-term survival and functional status of patients post-operatively."

interpret material from many sources for the benefit of their members. They set best practice standards and convey information about these standards to their membership on national and global level. Unlike government monopolies, these organizations operate by persuasion, not coercion.<sup>23</sup> Group members can use that information 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, others can pick up the slack.

The gains from creating these intermediaries dwarf the costs of their formation. And they can supply information that the FDA is too hidebound to provide. One of the key functions is of course to have long-term follow-up for treatment, which is a private substitute for the post-marketing review that the FDA has only fitfully undertaken. These groups can process information so that standardized practices can be altered incrementally in response to new findings. These groups are formed with respect to virtually every specialty and, in turn, break down their activities by subspecialties. They have budgets, organized subcommittees, extensive websites, and a clear mission and proven ability to communicate information about both adverse events and successful breakthroughs within days, even hours, of the time it is first acquired. And they work hard to make their own data bases interactive.<sup>24</sup>

These intermediate institutions are of special importance because of the peculiar structure of the US food and drug laws, which create a sharp distinction between permitted (as it were on-label) drug uses that the manufacturer is permitted to promote and those off-label uses of drugs that their manufacturers cannot promote, even if they use information that been published and disseminated on their web site or in established

---

<sup>23</sup> I ignore here standards that allow for interoperability of certain equipment, which must be followed by all to work. The treatment of individual patients does not raise these formidable complications here.

<sup>24</sup> The Society of Thoracic Surgeons notes that one of its aims is to “Link STS data with other subspecialty databases, including the American College of Cardiology National Cardiovascular Data Registry (NCDR) and the Virtual Pediatric Intensive Care Unit Database System (VPS Database) of the Pediatric Cardiac Intensive Care Society.” <http://www.ctsnet.org/announcements/announcement705.html>.

journals.<sup>25</sup> The situation in question creates an explicit legal no-man's land. If a drug is not approved for any use at all, off-label uses can never be tried, at immense social cost. As that is the case, the only sources of information available are those from the clinical trials. But once the drug is approved for one use, all off-label uses lie within the ambit of physicians and hospitals, to be decided on collectively or individually as they see fit given that the FDA has no power to regulate medical practice.

Off-label uses are a staple of cancer treatment. Clinical trials have never been cheap and in recent years they have become even more expensive, as the FDA under prodding from Congress has added still more requirements.<sup>26</sup> One consequence of the shift in policy is that drug owners are reluctant to run clinical trials for new indications. Many physicians are reluctant to include patients in clinical trials when they hold the conviction that they are both safe (enough) and effective (enough). Why subject a large portion of a very sick population to clinical trials in the face of prior experience that suggests that off-label use is likely to prove more advantageous than any other available treatment? Indeed, there are in many cases strong reasons why no one wants to undertake arduous clinical trials for these off-label uses. First of all, patients are either unwilling or unable to participate in these trials. Far from letting people get available drugs, clinical trials increase the odds of getting some substitute. How could a physician persuade sick patients to take real risks for social benefits? Second, firms have no financial incentive to undertake them. A standard drug or treatment has a limited patent life that starts to run long before commercialization. Typically, off-label uses proliferate only in rare circumstances—using Thalomid for multiple myeloma is a conspicuous one—as the result of regular clinical trials. The accumulation of information about off-label uses takes additional time, during which the patent clock keeps running. Why should any

---

25 Food, Drug and Cosmetic Act, 29 U.S.C. § 301 (2000). For discussion of the many complications, see Sandra Johnson, *Polluting Medical Judgment? False Assumptions in the Pursuit of False Claims Relating to Off-Label Prescribing, Marketing, and Research*, Minn. J. L. Science & Technology (forthcoming).

<sup>26</sup> See, for a recent account, Steve Usdin, *Regulation: System Reset in 2008*, 16 (No. 4) *BioCentury A1* (January 21, 2008).

patentee spend a fortune on clinical trials for a drug that will go generic shortly after they are completed? Only a longer patent life could change this behavior.

Notwithstanding these difficulties, in the cancer arena off-label use do *not* fall into a void because all forms of treatment are monitored closely by the National Comprehensive Cancer Network (NCCN) whose web site (<http://www.nccn.org/>) offers extensive information about clinical practice guidelines for various cancers, including off-label uses. The exact content of these guidelines does not lie in my competence to assess, but the entire process shows that the alternative to the present FDA regulation is not decisions by isolated physicians, but extensive collaborative efforts.

Here is one example. One click of the mouse takes the reader to NCCN Updates on breast cancer guidelines that offer insights on how to treat inflammatory breast cancer, which is described as both “rare” and “aggressive.”<sup>27</sup> There is nothing exceptional in publishing a notice about adding a new section of treatment guidelines. Yet the use of these two words, rare and aggressive, gives some indication as to the importance of the voluntary transmission of information. Aggressive cancers obviously need attention, but a small practice group finds it difficult to gather information in quantity about rare conditions. Yet a national (or even global) network should be able to accumulate information on treatment of rare diseases by publishing information more rapidly than any government agency, which could not tap easily into global sources.

One major concern with off-label uses is that they do not meet the FDA gold standard by which other products are judged. Implicit in this argument is that big science under centralized control outperforms the voluntary organizations now in place. The point seems misplaced. Today’s dual systems of regulation, coercive and voluntary, come from the clear recognition that the FDA cannot supply sufficient information that keeps pace with the advances in medicine. Indeed, I have heard more than one specialist physician moan in frustration (and always off the record) that FDA warnings and guidelines have “nothing to do” with good medical practice.

Yet, some die-hards continue to champion full-scale clinical trials before allowing drugs into general use. Thus I have been chastised as follows: “Does Epstein really not

---

<sup>27</sup> NCCN Updates Breast Cancer Guidelines, <http://www.nccn.org/about/news/newsinfo.asp?NewsID=127> (1/22/08).

understand that properly designed and conducted clinical trials are now universally accepted as the most reliable means of determining the effectiveness of a drug?” Or that “clinical trials . . . changed the basis for the use of drugs from something akin to hearsay and witchcraft to something much closer to science.”<sup>28</sup> No one, of course, wants to ban clinical trials, which may well be demanded privately in an unregulated system. Nonetheless, there are real difficulties in insisting clinical trials should be strictly required for all new drug uses. These trials do not start at the convenience of the individuals who might like to participate in them. What should a patient do if no trial is open? Here, again, the expected value calculations matter. “Reliable” is often too late for an individual. “Quick and dirty” can easily be better for the individual who is interested in maximizing his or her expected chances of survival.

The right question to ask is how much does any person have to forego in order to participate in a clinical trial. Those costs necessarily go down in light of the alternative avenues to obtain information through the NCCN or similar organizations. In particular, it would be instructive to know how many off-label uses were modified or discontinued in light of reports of poor performance that were reported through the NCCN or other voluntary associations. In addition, it would be instructive to learn what is the level of performance for those off-label uses that have worked their way into common practice, often constituting the majority of uses of particular drugs, all without going through any standard clinical trials. All off-label uses involve drugs that have passed Phase I clinical trials, so that high toxicity is not a real risk. The *accumulated* information for multiple uses could easily prove more reliable than any clinical trial done, necessarily and at great expense, on a smaller sample. Rational people seeking to maximize their expected value should take their chances on off-label uses, and they do every day. It is not clear that they give up anything at all. Yet another useful type of study would compare information about a drug that has both an 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. It would be of further value to run systematic studies examining the level of responsiveness of the NCCN and similar organization to new information, including that on adverse events, and

---

<sup>28</sup> Arnold S. Relman, To Lose Trust, Every Day, The New Republic, July 2, 2007, at 36.

to compare that speed to the FDA's. The options on updating are many: the treatment protocols could be changed so as to reduce the level of utilization relative to other products. Additional warnings and contraindications could be added, all in the same incremental fashion. My own guess is that the staple long-term uses will be beneficial, even without formal approval. Put otherwise, I suspect that off-label uses are as effective and safe as the on-label uses, both for a particular drug and for the class of drugs that have both types of use. If that hypothesis should prove true, it discredits any claim that clinical trials count as the gold standard for measuring safety and effectiveness. If it is false, we should expect to see a slow and steady decline in off-label uses.

**V. Centralized versus Decentralized Knowledge** In large measure, the strength of this claim depends on a theory of knowledge acquisition. The current clinical trial FDA model represents a view of top-down knowledge, which accepts, almost on blind faith, that the centralized collection and evaluation of information dominates the decentralized methods of collection and evaluation. In effect, the FDA works on a modern central planning paradigm of the sort that F.A. Hayek criticized so effectively in his writings on the subject.<sup>29</sup> The point of the counterattack is that single sources of control lack the redundancy to correct error, stifle the initiative that will make for new advantages, and are unable to coordinate and assemble information that is held in discrete packets by private individuals, some of which can be communicated through the price system, and other through voluntary sharing.

There is ample reason to think that Hayek's diagnosis accurately captures the lumbering condition of today's FDA. There is no reason to turn to the FDA's critics to make the point. Its responsible defenders note that even the recent statutory reforms<sup>30</sup>

---

<sup>29</sup> F. A. v. Hayek, *Socialist Calculation: The Competitive 'Solution,'* 7 *Economica* 125 (1940); F. A. Hayek, *The Use of Knowledge in Society,* 35 *Am. Econ. Rev.* 519 (1945). For my approach to limited knowledge, more generally, see Richard A. Epstein, *The Uses and Limits of Local Knowledge: A Cautionary Note on Hayek,* 1 *NYU Journal of Law & Liberty* 205 (2005); Richard A. Epstein, *Intuition, Custom, and Protocol: How To Make Sound Decisions With Limited Knowledge,* 2 *N.Y.U. Law & Liberty* 1 (2005).

<sup>30</sup> See, *The Food and Drug Administration Amendments Act of 2007,* Pub. L. No. 10-85, 121 Stat. 823 (2007).

have left the FDA “chronically under-funded,”<sup>31</sup> particularly in the post-marketing surveillance at which the NCCN excels. There is also official worry that the FDA cannot meet the appropriate scientific standards in today’s fast moving world with the rise of new scientific fields and techniques.<sup>32</sup> The common response to these rigidities is to act as though the problem is budgetary and not structural. Accordingly, the usual response attacks “inadequate funding” by asking for more.<sup>33</sup> Yet the more fundamental question, whether *any* centralized agency can be nimble enough to process information, is never asked. On this score, the dismal history of central planning in every other sector suggests that no modest reform that takes place within the current FDA framework is likely to improve overall agency performance. This gloomy prediction does not constitute a judgment about the competence or good will of individual FDA scientists. It rests on the permanent risk of permititis, or fundamental conviction that the current regulatory structure that gives too much power to too few individuals.

To make the point more directly, one key consequence of FDA monopoly power is to *slow down* the dissemination of information of various forms of drug treatment—something which rightly concerns the FDA. Recently, the FDA has floated the idea that it will allow drug companies to disseminate information about off-label uses that have appeared in peer-reviewed journals.<sup>34</sup> The proposal has predictably met with resistance from the adherents of the centralized model who think that the FDA should keep sole

---

<sup>31</sup> See also Kessler & Vladeck, at 472. For support, see Institute of Medicine of the National Academy, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* (Alina Baci, Kathleen Stratton & Shelia P. Burke, eds., 2006).

<sup>32</sup> FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology, 3.1 (February 2008).

<sup>33</sup> Id. at 1.3. page 10.

<sup>34</sup> FDA Proposes Guidance for Dissemination of Information on Unapproved Uses of Medical Products, <http://www.fda.gov/bbs/topics/NEWS/2008/NEW01798.html>, February 15, 2008, limiting the proposal to peer-reviewed journals with editorial boards that have conflict of interest policies, which means virtually all journals. See Anna Wilde Mathews & Avery Johnson, Boost for Off-Label Drug Use; FDA Would Let Firms Keep Doctors Informed on Unapproved Methods, Wall Street Journal, February 16, 2008, at A3.

control over the flow of information with respect to drugs. In light of the general observations on decentralized production of information, that position seems clearly to be wrong. The first point is that the mere fact that reputable journals publish clinical studies on off-label uses shows that we have developed an extensive gray market, which is better than no market at all, even if clearly inferior to the so-called “white market.” The existence of these markets is always a sign of dysfunction and the ability to get the information out matters. Second, the distribution of these peer reviewed studies helps answer many of the reservations to the FDA system, which necessarily has to run its clinical trials on limited populations.

Allowing the peer reviewed articles to be circulated increases, of course, the availability of *independent* knowledge about drugs. Ironically, in this regard, the FDA proposal to allow only the drug manufacturers to distribute the information introduces an avoidable bias if the company chooses to use selective release. Far better would be for the FDA to post *all* the information, favorable and unfavorable, on its own web sites, to insure its dissemination and worry more about saving lives than being sure that promotion and posting is not taken as an impermissible implied promotion of an off-label product. Better still would be a rule that allowed the companies in question to promote established off-label uses. Marketing makes a huge difference because companies know how to sell in ways that learned societies do not. Thus the FDA recently allowed the accelerated market approval of Avastin (bevacizumah) for breast cancer, which resulted in an immediate eight-percent increase in the market value of its manufacturer Genentech.<sup>35</sup> The key advantage is that accelerated market approval means that Genentech can market its product for the new use, which is likely to lead to much more rapid information dissemination than the NCCN can supply. No one doubts that Genentech gains hundreds of millions of dollars from the FDA decision. But it is important to remember that its increase in market value *understates* the social gain that comes from the FDA action, for that increase in share value does not include the anticipated consumer surplus (subjective value less market price) to the product users.

---

<sup>35</sup> Andrew Pollock, Wider Use of Avastin Is Approved, *New York Times*, February 23, 2008, at B1; Marilyn Chase & Anna Wilde Mathews, Genentech Clears Hurdle On Cancer Drug Avastin, *Wall Street Journal*, Fe. 23-24, 2008, at A3.

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.

**VI. The FDA Decisions on Cancer Drugs** The relative theoretical competence of these two alternative systems is borne out by a closer examination of the FDA's decisionmaking processes. At the most general level, it is important to stress anew the enormous power that the capacity to issue permits put into the hands of administrative officials. In any permit system, the burden lies on the individual applicant to show that the product in question meets all safety standards that are imposed by the government, even when the product is to be used by a competent and informed party.<sup>36</sup> That rule contrasts sharply with the standard judicial rule that injunctions against actions that might harm *other persons* should typically be issued only upon a showing of an imminent risk of a serious harm. Thus the permit system gives public officials far greater power than the standard form of injunctive relief, even though the circumstances justifying its exercise are weaker.

The scope of the administrative grant is far in excess of any ability of the FDA to discharge its obligations, as it is now agreed on all sides of the debate that the agency lacks the resources or expertise needed to evaluate cutting-edge scientific technologies. But the difficulties with the situation do not stop with this endemic problem. Two other issues, each illustrated by recent developments in the field, are also worthy of note. These involve, first, the articulation of standards for intelligent judgment, and, second, the risk of influence from powerful political or economic interests. Let us consider these in order.

*Standards of judgment.* One characteristic of any ban is that it has to draw sharp lines between those products that are let onto the market and those which are kept off. The difficulty is that any estimation of safety and effectiveness necessarily lies on a two-dimensional continuum so that it is well nigh impossible to draw sharp and defensible lines between those cases where a ban is desirable and those in which it is not. In

---

<sup>36</sup> For further discussion, see Richard A. Epstein, *The Permit Power Meets the Constitution*, 81 Iowa L. Rev. 407 (1995).

addition, any revision of initial decision is necessarily subject to similar difficulties. This problem is not faced by any voluntary organization that does not have the power to ban, but only to advise. In close cases, voluntary organizations can report all divisions of note, and allow members to make their own judgments. The likely response in those settings is that some oncologists and their patients will follow one course, and some another, depending at least on their own independent evaluation of the evidence, the medical condition of the patient, and the patient's attitude toward risk. Clearly other factors are likely to be involved, but those complexities do not alter this basic conclusion. The effect of a divided evaluation of a particular drug means that some physician-patient pairs will opt in for some use of the agent, and others will not. The uses in question might not be uniform, but most critically those subsequent choices can then be evaluated in order to update the assessment of the particular product. Thereafter, everyone can make timely revisions of their initial decisions. We should expect to see use decline when the early findings are bad, but to increase when they are good. In addition, as more data comes in, we should expect that the protocols and the counterindications will become clearer, allowing for a greater convergence over time. These decentralized adjustments are far less vulnerable to the peculiar preferences (or prejudices) of a single FDA committee. Use increases, revenues move upward, and research takes place, precisely because the bottleneck created by the FDA's permit power is removed. Smooth variations, not abrupt changes characterize the overall market place.

There is a second large difference between centralized and decentralized means of control. Centralized systems must always rely on objective measures to decide which products are let into the marketplace and which are not. They cannot enter into complex and subtle tradeoffs. Not surprisingly, the FDA prefers to rely on easily measured variables, most notably the extension of life. At the same time, the FDA has to ignore the variations in response for different patients, by basing its decision on average responses, which tends to deny licensing approvals to products that serve only a fraction of the overall population, as is the case with its contentious decision to limit the use of Iressa.<sup>37</sup>

---

<sup>37</sup> For discussion, see Richard A. Epstein, *Overdose: How Excessive Government Regulation Stifles Pharmaceutical Innovation* 135-138 (2006).

This administrative pressure, which is also found in judicial systems of social control,<sup>38</sup> is at constant tension with the desire to protect the autonomous choice of patients.

The severity of these regulatory conflicts is well revealed by the recent FDA decision to grant, over much opposition, Genentech an accelerated approval to promote and sell the drug for breast cancer patients. The vote in the FDA advisory committee was 5-4 against the use of the drug, and if that recommendation had been followed, the 38,000 or so women eligible for treatment would have been denied all (on-label) use, and the share price would not have moved up. In the regulatory system, so much can hang on a single vote. But the opposite is true in any decentralized system, where both sides can register their best judgment, while leaving it for downstream users to decide whether or not to use the treatment. In any decentralized setting, we can predict that a 5-4 against the use by a learned committee would on average result in fewer users than a 5-4 vote in favor. But that difference is likely to be small. The same could be said of the marginal adjustments for a 6-3 vote in either direction.

So who then is right? The answer is that no one is really sure. The evidence suggests that the use of Avastin in conjunction with the well-established drug Taxol delayed tumor progression for about 5.5 months longer than the use of Taxol alone—a clear plus. Yet, by the same token, the drug did not prolong life by any significant measure and had (as we might expect of any double dosages) more adverse side effects than Taxol alone. In this setting we can see why the FDA might incline against the use of Avastin because the objective measures do not stack up well in the comparison trials. But so what? One of the reasons why the twin principles of full disclosure and informed consent have gained such traction is that they pay respect to subjective preferences on questions concerning the quality of life. Within a decentralized system, the downward push of information means that everyone can take all this into account seamlessly. If, as is the case, physicians are “split” over the use of Avastin, then their patients should be as

---

<sup>38</sup> See, e.g., *Canterbury v. Spence*, 464 F.2d 772 (D.C. Cir. 1972), relying on objective measures of causation to see whether autonomous individuals would have altered their behavior in ways sufficient to avoid harm if they had been supplied full information. See also, Peter Schuck, *Rethinking Informed Consent*, 1903 Yale L.J. 899, 957-958 (1994), noting the tension between the respect for autonomous decisionmaking and the prudent person standard for disclosure.

well. The last thing that we need in close cases is an administrative decision that converts a 5-4 vote against into a legal regime in which none can use. Yet note this asymmetry: a vote of 5-4 in favor does not mean that all are bound to use the drug, only that those who choose to can. The distribution and interpretation of information, then, cut strongly in favor of a decentralized system that relies on persuasion.

*External influences* The question of whether a permit should issue is not of concern only to the product applicant and its potential customers. It is also matters to politicians who campaign over the FDA and competitors, who stand to lose sales if a rival product reaches a market in which they hope to exert a dominant position. On the first question, the FDA is subject to constant political pressure, such as the nonstop attacks of Senator Grassley on the ineffective protection that the FDA renders to consumers. Yet other political actors are reluctant to attack a senator whose support might be needed on other health care issues, in this case Medicare reform.<sup>39</sup>

On the economic side, the stakes are also enormous. If a second drug in a given class enters the market, it undercuts the monopoly obtained by the first to enter. Even in a duopoly situation, it would not be uncommon to see unit prices fall by 30 percent or more in markets where sales could amount of tens, even hundreds, of millions per year. It is therefore not surprising for competitors to take steps to torpedo the applications of their rivals, some of whom are already on the market and others of whom are in development. One recent illustration of this sort involves the FDA decision to delay, for more tests of course, approval of the cancer vaccine Provenge, which had shown promising results on certain classes (androgen-independent) of prostate cancers.<sup>40</sup> The FDA decision was roundly attacked in thousands of letters by angry persons who thought that this vaccine held out some last hope. The Nature Biotechnology report was that the delays in approval, over the advice of an advisory committee, were triggered in part by a critical letter from Howard Scher of Memorial Sloan-Kettering Cancer Center, who had

---

<sup>39</sup> See Usdin, System Reset, at 2.

<sup>40</sup> For a recounting of the events on which this section relies, see Editorial, The Regulator Disapproves, 26 Nature Biotechnology (No. 1) 1 (January, 2008).

an undisclosed financial interest in a rival drug Asentar, produced by a firm called ProQuest on whose medical board Scher sat.

All conflict of interest regulations, of course, rightly require the routine disclosure of these connections, so that public authorities could have discounted the claims made in that and similar letters if they so chose. But even if these disclosures were made, the question of undue influence still remains. Unfortunately, permititis makes the entire information system more vulnerable to subversion than the NCCN and similar voluntary organizations, where no small group has power to subvert any new or experimental drug. Improper evidence could of course mislead NCCN members. But any harm in question is cabined because those board members do not have the power to issue bans, and it can be quickly counteracted without further administrative action. The redundancy of decentralized information systems makes them resistant to the political maneuvers that always take place when government official can exercise the permit power.

**Conclusion** This paper is a conscious outlier from the presentations that will follow. It does not ask the question of *how* the FDA should exercise its permit powers. Rather it asks the prior question of *whether* it should have those powers at all. In it, I start from a general political theory whose strong initial presumption is against the use of the permit power to regulate the decisions that autonomous individuals make in their own lives. It then examines FDA activities to identify some sufficient reason to overcome that presumption. The search is futile. One standard justification for the use of state power is clearly not available in this context, namely, the protection of other individuals against the risk of force and fraud. Whatever else the FDA regulates, it does not deal with public nuisances or environmental risks.

The inquiry next turns to whether the FDA can engage in a form of consumer protection against the hasty and unwise choices that people undoubtedly make in their own life. It would be foolish to dismiss this risk on the grounds that all individuals are imbued with a natural talent to make only rational choices. Even if that point is fully accepted, it hardly points to granting the FDA unquestioned permit power in all sorts of cases. The first point here is that the mode of distribution of drugs matters. There is a greater concern about impulsive, habitual, or otherwise foolish behavior when individuals have direct access to certain drugs. Even here, we should be highly cautious about bans,

but could at least entertain the possibility. But in all cases cancer drugs are only distributed through professional intermediaries with access to huge amounts of personal and group information. These organizations have, of course, an extensive role to play right now even though the FDA exercises a strong gatekeeper function. Allowing one on-label use does not decide whether it should be used, 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 to draw from the present situation is this: the voluntary mechanisms that work right now for both on-label and off-label uses should be able to work across the board. This is not a case where two systems of control are better than one. Rather, it is more likely that public investments in the FDA's permit power yields a negative return. Sounder decisions are more likely to be made with decentralized bodies. As information is collated and presented, we should expect to see slow shifts in uses and behaviors under a legal regime that facilitates continuous updating and experimentation. Even if the FDA could acquire additional resources, it could not discharge its chosen mission since, at any resource level, it comes out second best relative to the private systems that are available. It would still underestimate the risks of delay. It would still ignore variation across individual cases. It would still be vulnerable to enormous political and economic pressures. The FDA's permit power is an open wound in the body politic. Permittitis cannot be controlled. It should be eliminated.