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Restricting Access to Unapproved Drugs: A Compelling Government Interest

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RESTRICTING ACCESS TO UNAPPROVED DRUGS:
A COMPELLING GOVERNMENT INTEREST?

PETER M. CURRIE*

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I. INTRODUCTION

The prospective review and approval of drugs is central to the public health mission of the United States Food and Drug Administration (FDA). Requiring pharmaceutical manufacturers to generate information about their products' safety and efficacy enables the agency to evaluate the risks and benefits associated with their use, thereby preventing overly harmful products from reaching the market. The majority of consumers benefit from this intervention by gaining access to an array of drugs that are proven to be safe and effective. Thus, governmental regulation in this area is arguably justified because the aggregate social welfare is substantially improved.

However, this majoritarian view overlooks the concentrated costs that the drug approval process imposes upon minority groups within society. Drug testing is both resource intensive and time consuming, with an average of eight years required for human clinical testing alone.¹ For individuals suffering from terminal illness who

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¹Christopher P. Adams & Van V. Brantner, *New Drug Development: Estimating Entry from Human Clinical Trials* 9 (Federal Trade Comm'n Bureau of Economics, Working Paper

have exhausted conventional therapies, this delay in access can be fatal. Many terminally ill patients are therefore willing to tolerate vastly greater therapeutic risks in an effort to find a cure. Under the current regulatory structure, however, willingness to tolerate risk does not necessarily translate into access to unapproved drugs.

The tension between drug safety and access to developing experimental drugs most recently came to the forefront in 2003, when the Abigail Alliance for Better Access to Developmental Drugs [hereinafter Abigail Alliance]² brought suit to enjoin the FDA from enforcing its current policy banning the use of post-Phase I investigational drugs by terminally ill patients excluded from Phase II clinical trials.³ The Court of Appeals for the D.C. Circuit recognized a constitutional substantive due process right “to access potentially life-sustaining medication where there are no alternative government-approved treatment options.”⁴ After concluding that the right asserted by Abigail Alliance merits due process protection, the court remanded the case to the district court to determine whether the FDA’s current policy withstands the application of the rigorous strict scrutiny review, essentially, to determine whether the policy is narrowly tailored to serve a compelling governmental interest.⁵

This article analyzes whether the government has a compelling interest in preventing mentally competent, terminally ill patients from accessing post-Phase I drugs. Part II reviews the history of FDA drug regulation and summarizes current law pertaining to the drug approval process. Part III considers whether, in light of the constitutional right recognized by the D.C. Circuit, the government’s interest in public health can validate restrictions on drug access for terminally ill patients. More specifically, Part III examines whether such restrictions can be justified either by the benefits they confer upon terminally ill patients themselves, or by the benefits they confer upon society at large. Finally, Part IV concludes by finding that both of these justifications fail, thereby undermining the government’s claim to a compelling interest in restricted drug access for this population.

II. FDA DRUG APPROVAL PROCESS

A. History

Federal regulation of drugs began with the Pure Food and Drug Act [hereinafter

No. 262, 2003), available at <http://www.ftc.gov/be/workpapers/wp262.pdf> (last visited June 2, 2007).

²Abigail Alliance is a non-profit organization that aims to help cancer patients and others with life-threatening illnesses through education and advocacy. See Abigail Alliance for Better Access to Developmental Drugs, The Abigail Alliance Mission, <http://abigail-alliance.org/mission.htm> (last visited Nov. 28, 2006).

³Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach, 445 F.3d 470, 472 (D.C. Cir. 2006).

⁴*Id.*

⁵*Id.* at 486. On November 21, 2006, the Court of Appeals for the D.C. Circuit granted the FDA’s Petition for Rehearing En Banc. See Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach, No. 04-5350, 2006 U.S. App. LEXIS 28974, *1 (D.C. Cir. Nov. 21, 2006).

PFDA].⁶ Enacted in 1906 in response to criticism of widespread food and drug impurities,⁷ this legislation established liability for the manufacture of adulterated⁸ or misbranded⁹ drugs by requiring manufacturers to monitor their products for strength, quality, and purity,¹⁰ and to provide complete and accurate labeling of drug contents.¹¹ However, the PFDA failed to set forth standards or specific methods of pre-market testing that would prevent adulteration, or to provide any mechanism for centralized regulatory approval of new drugs.¹²

The 1937 Elixir Sulfanilamide tragedy¹³ spurred Congress to take a more significant step toward a pre-market drug approval system. Towards that end, Congress passed the Food, Drug, and Cosmetic Act [hereinafter FDCA], which required safety testing and government approval of new drugs before commercial marketing.¹⁴ Under the provisions of the FDCA, prospective manufacturers were required to file applications for the sale of new drugs with the Secretary of Agriculture, describing drug components and composition, methods of production control, and proposed labeling language.¹⁵ The FDCA also required applicants to provide investigational safety reports and samples of the drugs under consideration.¹⁶

⁶Pure Food and Drug Act of 1906, ch. 3915 §§ 1-12, 34 Stat. 768, 768-772, *repealed by* 21 U.S.C § 329(a) (1938).

⁷Peter Barton Hutt, *Development of Federal Law Regulating Slack Fill and Deceptive Packaging of Food, Drugs, and Cosmetics*, 42 FOOD DRUG COSM. L.J. 1, 1-2 (1987). Although many factors precipitated passage of the 1906 Act, publication of Upton Sinclair's *The Jungle* played a significant role in generating the public outcry (and political will) needed to spur legislative action. *Id.* See also UPTON SINCLAIR, *THE JUNGLE* (1906).

⁸Pure Food and Drug Act § 7.

⁹*Id.* § 8.

¹⁰*Id.* §§ 1-12.

¹¹*Id.*

¹²The 1906 Act did authorize the Bureau of Chemistry of the Department of Agriculture to conduct compliance examinations of drugs. Pure Food and Drug Act § 4. However, this provision did not require pre-market approval and served merely as a tool for policing products already in the marketplace. *See id.*

¹³Sulfanilamide, a drug used to treat streptococcal infections, had been shown to have dramatic curative effects and had been used safely in tablet and powder form. In 1937, however the S.E. Massengill Co. began to produce a liquid form (Elixir Sulfanilamide) by dissolving the drug in diethylene glycol. The company laboratory tested the mixture for flavor, appearance, and fragrance and found it satisfactory. The company then sent shipments of the toxic mixture throughout the United States, ultimately causing the deaths of more than a hundred people. *See* Carol Ballentine, *Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident*, FDA CONSUMER MAG., June 1981, *available at* <http://www.fda.gov/oc/history/elixir.html>.

¹⁴Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301-392 (2000).

¹⁵21 U.S.C. § 355(b) (2000).

¹⁶*Id.*

Unless the Secretary of Agriculture rejected or postponed consideration of the application within sixty days of filing, default approval was conferred by statute.¹⁷

The final step in the evolution of modern drug regulation occurred in response to the thalidomide tragedy,¹⁸ after which Congress enacted the Kefauver-Harris Amendments [hereinafter 1962 Amendments].¹⁹ The 1962 Amendments required more rigorous pre-approval drug testing than was required under the original FDCA, instituting a series of clinical testing “phases” that comprise the norm under current law.²⁰ At present, the initial steps in obtaining FDA approval entail laboratory and animal testing to determine whether a drug is sufficiently safe and promising to justify human experimentation.²¹ Using evidence gathered in these preliminary tests to support safety and efficacy claims, the drug sponsor files an Investigational New Drug (IND) application, seeking FDA authorization to begin the process of testing on humans.²²

B. The Clinical Trial System

Although clinical trials are both expensive and time consuming, the process of submitting an IND for clinical testing approval is relatively straightforward. An IND application notifies the FDA that a company is about to initiate clinical trials and permits the FDA to conduct an initial assessment of the value of those trials on the basis of the information provided by the applicant.²³ If the IND application is granted, the sponsor is permitted to begin clinical experimentation on human subjects,²⁴ which is mandatory for final FDA approval of a drug.²⁵

¹⁷21 U.S.C. § 355 (1938).

¹⁸HARVEY TEFF & COLIN R. MUNRO, *THALIDOMIDE: THE LEGAL AFTERMATH* 1-10 (1976). Thalidomide, marketed as a sedative safe for use by pregnant women during the late 1950s and early 1960s, resulted in birth defects in thousands of infants in Europe. *Id.*

¹⁹U.S. Food and Drug Administration (FDA), *Drugs and Foods Under the 1938 Act and Its Amendments*, <http://www.fda.gov/oc/history/historyoffda/section3.html> (last visited Feb. 17, 2007).

²⁰21 C.F.R. § 312.21 (2000).

²¹U.S. Food and Drug Administration (FDA), *From Test Tube to Patient: Protecting America's Health Through Human Drugs*, A Special Report From the FDA Consumer Magazine and the FDA Center for Drug Evaluation and Research (Jan. 2006), available at <http://www.fda.gov/fdac/special/testtubetopatient/default.htm>.

²²David A. Kessler, *The Regulation of Investigational Drugs*, 320 *NEW ENG. J. MED.* 281, 281-82 (1989).

²³*Id.* The IND application must include the names of parties responsible for the investigation, a statement of the investigational plan, a statement of the name of the drug to be tested and all its active ingredients, a summary of any previous human experience with the drug, a description of the overall plan for investigation, identification of phases of clinical investigation, a list of possible risks and side effects, a protocol for each planned study, and a summary of pharmacological and toxicological effects of the drug on animals. 21 C.F.R. § 312.23 (2000).

²⁴*See id.* § 314.126 (listing the FDA requirements regarding clinical trial methodology).

²⁵21 U.S.C. § 355 (2000).

A three-phase process of testing on human subjects remains the FDA standard.²⁶ Phase I consists of initial safety testing, during which a relatively small sample of healthy, asymptomatic subjects receive the drug and are monitored for signs that the drug may be unsafe for humans.²⁷ If the results of Phase I indicate that the drug may be safe, the sponsor proceeds to Phase II, during which both the safety and efficacy of the drug are examined through controlled experimentation upon a larger sample of symptomatic subjects.²⁸ If the results from Phase II are promising, a much larger sample is used in Phase III to further assess safety and efficacy.²⁹

If the results of clinical testing are promising through Phase III, the IND sponsor may decide to continue seeking FDA approval by submitting a New Drug Application (NDA), which provides the FDA with information that includes the data collected and analyzed during experimentation.³⁰ Within 180 days, the FDA must approve the application or notify the applicant of the opportunity to request a hearing on the merits of the application.³¹ If granted, FDA approval is promised upon proof of the safety and efficacy of the drug when used for the “on-label” purposes stipulated by the drug’s sponsor.³²

C. Expanded Access Programs

In an effort to balance the government’s interest in drug safety and efficacy with terminally ill patients’ interest in gaining rapid access to promising therapies, the FDA has carved out several exceptions to the clinical trial testing process described above.³³ These exceptions fall into one of two categories: expanded access (whereby some patients gain access to drugs before approval) and expedited review (in which

²⁶21 C.F.R. § 312.21 (2000).

²⁷*Id.* § 312.21(a). For cancer drugs, which are highly toxic, Phase I studies are normally restricted to persons with cancer who have failed all other available therapies.

²⁸*Id.* § 312.22(b).

²⁹*Id.* § 312.22(c). In addition, a fourth and final phase may follow drug approval. Phase IV consists of post-approval monitoring of drugs after they have been placed on the market. Phase IV testing can be required by the FDA to measure the safety and efficacy of approved drugs on an ongoing basis and to reevaluate drugs in light of developing scientific and medical knowledge. *Id.* § 312.85.

³⁰*See* 21 U.S.C. § 355(b)(1)(A) (2000). The NDA contains data demonstrating “whether or not such drug is safe for use and whether such drug is effective in use.” *Id.*

³¹21 U.S.C. § 355(c)(1)(A) & (B) (2000).

³²*Id.* § 355(d). The 1962 Amendments require “substantial evidence . . . consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have. . . .” *Id.*

³³*See* U.S. Food and Drug Administration (FDA), Expanded Access and Expedited Approval of New Therapies Related to HIV/AIDS, <http://www.fda.gov/oashi/aids/expanded.html> (last visited Nov. 9, 2006). The majority of these exceptions arose in response to activism and political pressure during the early years of the AIDS epidemic, and several are limited specifically to therapies for HIV/AIDS. *Id.*

the approval process itself is hastened or truncated).³⁴ Because drugs in the latter category receive FDA approval before market entry, only the expanded access exceptions are relevant to the analysis of a pre-approval right to access; thus, the exceptions in this category are outlined below.

1. Treatment IND

In 1987, the FDA enacted “Treatment IND” provisions that formalized expanded access procedures for patients suffering from serious or life-threatening diseases in the absence of satisfactory approved alternative drugs or therapies.³⁵ Under these provisions, a drug manufacturer may apply to the FDA for permission to distribute a promising investigational therapy prior to final approval if:

- (i) The drug is intended to treat a serious or immediately life-threatening disease; (ii) there is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population; (iii) the drug is under investigation in a controlled clinical trial, under an IND in effect for the trial, or all clinical trials have been completed; and (iv) the sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.³⁶

Treatment INDs are a viable option for serious diseases during or after Phase III investigation and in some situations may be granted as early as Phase II.³⁷ For immediately life-threatening diseases, Treatment INDs are available “[e]arlier than Phase III, but ordinarily not earlier than Phase II.”³⁸ Although no statutory requirements exist for data collection and reporting under Treatment INDs, the FDA routinely requires administration of the experimental drug to be monitored for safety.³⁹

2. Group C Treatment IND

The FDA and the National Cancer Institute (NCI) established the Group C Treatment IND, in which the drugs are distributed only by the National Institutes of

³⁴*Id.*

³⁵Investigational New Drug, Antibiotic, and Biological Drug Product Regulations, 52 Fed. Reg. 8,850 (proposed Mar. 19, 1987) (codified at 21 C.F.R. § 312.34); 52 Fed. Reg. 19,466 (proposed May 22, 1987) (codified at 21 C.F.R. 312.34). Immediately life-threatening diseases are those for “[w]hich there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.” 21 C.F.R. § 312.34(b)(3)(ii) (2000).

³⁶21 C.F.R. § 312.34(b)(1) (2000).

³⁷*Id.* § 312.34(a). As an additional mode of access the FDA reserves the authority to approve applications for compassionate use INDs on a case-by-case basis. *Id.* § 312.36.

³⁸*Id.* § 312.34(a). However, in practice the Treatment IND usually functions as a bridge between the completion of controlled studies and final marketing approval. *Id.*

³⁹Ezekiel J. Emanuel, *Drug Addiction*, THE NEW REPUBLIC, July 3, 2006, at 9.

Health (NIH) under NCI protocols.⁴⁰ Group C Treatment IND allows for oncologists to obtain investigational agents for treating cancer outside the controlled clinical trials.⁴¹ The drugs in this category are usually Phase III study drugs which show “evidence of relative and reproducible efficacy in a specific tumor type.”⁴² Properly trained physicians can administer these drugs without specialized supportive care facilities.⁴³ While patients treated under these guidelines are not participants in a clinical trial, data on safety and effectiveness are still collected.⁴⁴ Unlike Treatment IND, which is available for experimental drugs intended to treat *any* serious or life-threatening disease for which approved therapies are unavailable, the Group C Treatment IND is a means for the compassionate distribution of investigational agents for the treatment of cancer outside the controlled clinical trial setting.

3. Emergency Use IND

Both Treatment IND and Group C Treatment IND contain procedural requirements that must be met before experimental drugs are made available. However, the need for an investigational drug may arise in an emergency situation that does not allow time for procedural compliance. If an emergency situation does arise, the FDA can authorize the shipment of these drugs for a particular use.⁴⁵ But, the authorization is conditional on whether the sponsor files an appropriate application as soon as possible.⁴⁶

4. Parallel Track

In 1992, the Public Health Service (PHS) issued a Policy Statement providing for expanded availability of INDs for the treatment of AIDS and other HIV-related diseases through a “parallel track” mechanism.⁴⁷ Parallel track studies run concurrently with traditional studies, but can be conducted without the use of experimental controls.⁴⁸ The vehicle of sub-experimental quality trials expands access to experimental drugs to those who cannot be included in the limited number of slots available in the concurrent clinical investigation.

Collectively, these expanded access programs constitute an effort by the FDA to respond to the interests of terminally ill patients. Nonetheless, many – including the patients Abigail Alliance represents – contend that these reforms are insufficient. To

⁴⁰ U.S. Food and Drug Administration (FDA), Guidance for Institutional Review Boards and Clinical Investigators: 1998 Update, <http://www.fda.gov/oc/ohrt/irbs/drugsbiologics.html#treatment> (last visited Dec. 8, 2006).

⁴¹*Id.*

⁴²*Id.*

⁴³*Id.*

⁴⁴*Id.*

⁴⁵*Id.* See also 21 C.F.R. § 312.36 (2000).

⁴⁶See FDA, Guidance for Institutional Review Boards, *supra* note 40.

⁴⁷57 Fed. Reg. 13,250 (Apr. 15, 1992). While the logic of a parallel track could be applied to other diseases, the PHS Policy is limited to AIDS and other HIV-related diseases.

⁴⁸57 Fed. Reg. 13,250, 13, PALTROW, COHEN & CAREY, 256 (Apr. 15, 1992).

determine whether further relaxation of the drug approval process is constitutionally mandated, it is necessary to examine and evaluate the competing individual and government interests at stake.

III. BALANCING INDIVIDUAL RIGHTS WITH STATE PROMOTION OF PUBLIC HEALTH

It is widely accepted that the government has a strong interest in protecting the public's health, one that the FDA may legitimately manifest through the drug approval process described above.⁴⁹ Pre-market drug approval arguably serves this interest in two ways. By requiring a demonstration of safety, it prevents individuals from harming themselves by consuming medicines that are essentially poisonous, and it ensures that patients do not forgo effective therapies in favor of impotent "snake oils."⁵⁰ Conversely, deviation from the drug approval process would arguably threaten the government's public health interest in two ways. Patients who take drugs with only minimal safety information are at much greater risk of self-induced injury. Additionally, it is hypothesized that a market for unapproved drugs will diminish the supply of eligible clinical trial candidates, thereby harming the ultimate beneficiaries of the clinical trial system.

However, for the government to restrict a fundamental constitutional right, it must assert not only a legitimate interest, but one that is *compelling*.⁵¹ This highest standard of review requires meaningful evidence that limitations on drug access for the terminally ill are likely to realize the benefits described above. To determine whether this standard is met, each of the justifications for government regulation must be examined.

A. *The Limits of Paternalistic Regulation*

Traditionally, paternalistic governmental regulation – that is, regulation of behavior that risks primarily the health or safety of the individual concerned – has been controversial in the United States.⁵² Examples of paternalistic regulation in the field of public health include mandatory motorcycle helmet and seatbelt use: from the public health perspective, these laws are justified because they improve a population's health by reducing behavioral risks.⁵³ Conversely, many argue that individuals should have the right to make their own decisions about behaviors that

⁴⁹See *Abigail Alliance for Better Access to Development Drugs v. Von Eschenbach*, 445 F.3d 470 (D.C. Cir. 2006).

⁵⁰The United States Supreme Court recognized this concern in *United States v. Rutherford*, noting, "if an individual suffering from a potentially fatal disease rejects conventional therapy in favor of a drug with no demonstrable curative properties, the consequences can be irreversible." *United States v. Rutherford*, 442 U.S. 544, 556 (1979) (citation omitted).

⁵¹See, e.g., *Roe v. Wade*, 410 U.S. 113, 155 (1973).

⁵²PROMOTING HEALTH: INTERVENTION STRATEGIES FROM SOCIAL AND BEHAVIORAL RESEARCH 398 (Brian D. Smedley & S. Leonard Syme eds., 2000), available at http://www.books.nap.edu/catalog.php?record_id=9939#toc (last visited June 2, 2007).

⁵³Lawrence O. Gostin, *Public Health Law in a New Century: Part III: Public Health Regulation: A Systematic Evaluation* 283 JAMA 3118, 3119 (2000).

primarily affect themselves.⁵⁴ Under this logic, a person chooses not to wear a seatbelt not because she is unaware of the risk, but presumably because that person places one value (freedom from restraint) above another (physical security). Legislatures and courts generally resolve this tension by balancing the benefits of state action against the burdens imposed.⁵⁵

Regulatory paternalism in the drug marketplace is generally justifiable under this balancing approach, in part due to the informational asymmetries that exist between transacting parties.⁵⁶ In the example outlined above, the motorist has all the information she needs to assess the risks and benefits associated with choosing not to wear a seatbelt. By contrast, consumers could never fully possess the expertise needed to evaluate the risks and benefits associated with pharmaceutical products due to their highly technical nature. The FDA corrects this information gap by requiring evidence of safety and efficacy as a condition of market entry, reducing the likelihood that consumers will unwittingly ingest harmful products.⁵⁷ Additionally, the drug approval process serves a risk management function, spreading incremental costs throughout society (in the form of restricted access) rather than allowing their concentration on small groups of individuals (in the form of catastrophic harm).⁵⁸ Hence any infringement of an individual liberty interest thus appears justified by both collective and individual benefits.

While this logic holds true for the healthy majority, it is unclear whether it applies to the minority of patients who are terminally ill and have exhausted all available therapies. The needs and preferences of the terminally ill depart systematically from those of the general public. By definition, such patients derive no present benefit from FDA regulation because no approved therapy can successfully treat their diseases. Furthermore, the potential for future benefit is only marginal for persons who may not live long enough for that benefit to be realized. For the terminally ill, restrictions on drug access, therefore, impose concentrated costs with little to no benefit. It follows that the basic premise of paternalistic regulation – that restrictions on liberty can be justified when in an individual's best interests – fails entirely in this context. Rather than promoting a compelling interest in the health of terminally ill patients, FDA restrictions on drug access appear only to deny this population a final chance for successful treatment.

Concededly, granting access to post-Phase I drugs does not guarantee that patients' lives will be extended. A recent meta-analysis of Phase I oncology trials found that approximately only ten percent of patients responded positively to the experimental therapy under investigation.⁵⁹ Furthermore, many clinical trial

⁵⁴Richard A. Epstein, *Let the Shoemaker Stick to His Last: A Defense of the "Old" Public Health*, 46 PERSP. BIOLOGY & MED. S138, S138-S159 (2003).

⁵⁵See Gostin, *supra* note 53, at 3118.

⁵⁶Michael D. Greenberg, *Information, Paternalism, and Rational Decision-Making: The Balance of FDA New Drug Approval*, 13 ALB. L.J. SCI. & TECH. 663, 671-74 (2003).

⁵⁷The Elixir Sulfanilamide tragedy serves as the paradigm case for this undesired outcome. See *supra* text accompanying note 13.

⁵⁸Greenberg, *supra* note 56, at 674-75.

⁵⁹Elizabeth Horstmann et al., *Risks and Benefits of Phase I Oncology Trials, 1991 Through 2002*, 352 NEW ENG. J. MED. 895, 899 (2005).

participants experience improved outcomes not because of the study drug, but because of the unusually high quality of ancillary care they receive in the research setting.⁶⁰ These ancillary benefits would not accrue to patients taking experimental drugs in the usual care setting. However, the question presented is not whether access to unapproved drugs will guarantee a health benefit to terminally ill patients. Rather, given that the court has recognized a right of access, the question is whether a compelling interest justifies government restrictions on that right. Concerns over treatment efficacy or effectiveness do not provide the requisite justification.

Even if FDA regulation provides few affirmative benefits to terminally ill patients, an important question remains: can the government maintain a compelling interest in protecting these individuals from self-induced harm? The fact that someone is terminally ill does not render his life worthless, nor does it eliminate his interest in attaining the highest possible quality of life. Consumption of drugs whose safety profile is only minimally understood could harm terminally ill patients by further shortening their lives or by causing significant morbidity. These risks are even more acute outside of the clinical trial setting, where close monitoring of subjects serves to mitigate the potential for iatrogenic harm. Arguably, the government's interest in the safety of *all* patients (not only those with a chance of long-term recovery) provides sufficient justification for restricting access to unapproved drugs.

This line of reasoning, while not without merit, fails for several reasons. For one, it establishes an indefensible double standard: terminally ill patients who qualify for clinical trials can access potentially harmful drugs, but those who do not qualify cannot. This differential treatment weakens the patient safety justification for restricted access, as the government is clearly willing to tolerate risk to patients in a controlled setting. While patients in the usual care setting may experience some increased risk due to the absence of close monitoring, it is far from clear that this increase is sufficient to justify restrictions on a constitutional right.

The patient safety argument is further undermined by the various expanded access programs described above, which make unapproved drugs available to patients in uncontrolled settings. Participants in those programs are exposed to the same drug-related risks as are subjects in clinical trials, but without the benefits of careful monitoring. The patient safety argument wrongly assumes that a denial of access is the least restrictive means to achieve the government's interest. To the contrary, a qualified form of post-Phase I access – e.g., requiring careful safety monitoring of patients taking the drug – would promote safety with less intrusion on patient rights.⁶¹

⁶⁰Clinical trials often deviate substantially from usual practice conditions in ways that benefit patients: providing free care, using specialized providers and settings, and maintaining high treatment compliance. See Kenneth B. Wells, *Treatment Research at the Crossroads: The Scientific Interface of Clinical Trials and Effectiveness Research*, 156 AM. J. PSYCHIATRY 5, 6 (1999).

⁶¹This would mirror current FDA practice with Treatment INDs, which are granted on the condition that the administration of the drug will be carefully monitored for safety. See Emanuel, *supra* note 39, at 12.

B. Safeguarding the Clinical Trial System

Government regulation of behavior with the potential to harm others has proved less contentious than paternalistic regulation, as it fits more comfortably within the liberal principles of the United States political framework.⁶² Many commentators have criticized the *Abigail Alliance* decision on “harm to others” grounds, arguing that the right recognized by the court poses a severe threat to the integrity of the drug testing process.⁶³ This argument posits that granting access to post-Phase I drugs outside of the clinical trial context will reduce incentives to participate in those trials, leaving researchers with insufficient numbers of subjects to generate statistically valid data. Consequently, this occurrence will either delay the drug development process or will pressure the FDA to approve drugs with incomplete knowledge about their safety and efficacy. Recent history suggests that these concerns are not entirely unfounded: the challenges associated with subject recruitment and retention are well documented,⁶⁴ while the highly publicized recall of COX-2 inhibitors such as Vioxx and Celebrex indicates that the FDA approval process is already under considerable strain.⁶⁵

However, it is far from clear that these fears justify government action to restrict the right to access post-Phase I experimental drugs. Critics of the court’s decision hypothesize a causal nexus between the newly established right and the parade of horrors described above, but neglect to address the myriad factors that mediate this relationship. The scope of the constitutional right, the motives prompting subjects to participate in clinical trials, and the willingness of pharmaceutical companies to market unapproved drugs will all influence the impact of the court’s decision on the drug testing process. Each of these factors must be scrutinized.

1. Scope of the Constitutional Right of Access

The degree of risk posed to the clinical trial system depends, first and foremost, upon the definition of the right in question. Remarkably, the *Abigail Alliance* opinion offers two different definitions, introducing a potentially troublesome element of ambiguity into the analysis.⁶⁶ In the first, which is the more expansive of the two, the Court of Appeals for the D.C. Circuit “carefully described” this right as that “of a mentally competent, terminally ill adult patient to access potentially life-saving post-Phase I investigational new drugs, upon a doctor's advice, even where

⁶²Peter Berkowitz, *The Court, the Constitution, and the Culture of Freedom*, 132 POL’Y REV. 3, 3 (2005). See also *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*, 445 F.3d 470 (D.C. Cir. 2006).

⁶³See, e.g., Emanuel, *supra* note 39, at 9-10; Susan Okie, *Access Before Approval – A Right to Take Experimental Drugs?*, 355 NEW ENG. J. MED. 437 (2006).

⁶⁴Nancy S. Sung et al., *Central Challenges Facing the National Clinical Research Enterprise*, 289 JAMA 1278, 1279-80 (2003).

⁶⁵*Ensuring Drug Safety: Where Do We Go From Here?: Hearing Before the S. Comm. on Health, Education, Labor, and Pensions*, 109th Cong. (2005) (statement of Bruce M. Psaty, Professor of Medicine, Epidemiology and Health Services, University of Washington).

⁶⁶*Abigail Alliance for Better Access to Development Drugs v. Von Eschenbach*, 445 F.3d 470 (D.C. Cir. 2006).

that medication carries risks for the patient.”⁶⁷ Yet in a later formulation, the court adopted a more restrictive approach: “where there are no alternative government-approved treatment options, a terminally ill, mentally competent adult patient’s informed access to potentially life-saving investigational new drugs determined by the FDA after Phase I trials to be sufficiently safe for expanded human trials warrants protection under the Due Process Clause.”⁶⁸

The distinction between a restricted and expansive formulation of the right is central to determining the weight of the government’s interest in regulating access to unapproved drugs. Under the restricted definition, a patient could gain access to unapproved drugs only if there were “no alternative government-approved treatment options.”⁶⁹ Because an IND is a form of government approval, this restriction would require patients to be declared ineligible for all relevant clinical trials as a precondition to the exercise of the right. By contrast, the more expansive definition would allow patients an unfettered choice between enrolling in a clinical trial and purchasing the desired medication on the open market. This increased access could discourage eligible candidates from participating in clinical trials, resulting in the structural harms hypothesized above.

In fact, there are several indications that the court’s holding should be interpreted to incorporate only the restricted definition. First, it conforms more precisely to the scope of the right of which plaintiffs sought recognition.⁷⁰ Furthermore, other sections of the opinion suggest that the court did not contemplate recognizing a right of access for patients eligible to participate in clinical trials.⁷¹ This evidence substantially weakens the argument for a compelling government interest based on potential harm to the clinical trial system, as it essentially leaves that system intact.

2. Research Subject Motivation

Assuming, *arguendo*, that an expansive reading of the right to access is correct, an important question remains: will terminally ill patients abandon clinical trials to obtain their medications on the private market? The answer depends in part upon the motives that influence an individual’s decision to participate as a subject of research. If clinical trial participants are motivated primarily by altruistic concerns, then

⁶⁷*Id.* at 472.

⁶⁸*Id.* at 486.

⁶⁹*Id.*

⁷⁰In its initial brief, Abigail Alliance argued that “the right [plaintiffs] claim would extend only to terminally ill patients who have no approved alternatives and are not able to participate in the clinical trials. (Patients who are able to participate in the clinical trials have an approved alternative – the trial – and hence no compelling constitutional claim.) Limited that way, the relief they seek could not and will not interfere with the clinical trial process.” Reply Brief of Petitioner-Appellant at 25-6, *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*, 445 F.3d 470 (D.C. Cir. 2006) (No. 04-5350).

⁷¹*See, e.g., Abigail Alliance for Better Access to Developmental Drugs*, 445 F.3d at 478 (noting that “[t]he FDA characterizes the Alliance’s claimed right as a broadly stated prerogative to access post-Phase I investigational new drugs and to receive treatment, but the Alliance has defined the right more narrowly . . . [, claiming only] the right of terminally ill patients, acting on a doctor’s advice, to obtain potentially life-saving medication when no alternative treatment approved by the government is available”).

increased access to unapproved drugs seems unlikely to alter current recruitment and retention patterns. Conversely, if intrinsic motivations are paramount, then the creation of a market for experimental drugs could substantially decrease the pool of potential subjects.

Research data on this topic are limited, but at first glance it appears that the binary distinction drawn above between intrinsic and extrinsic motives is rejected. Subjects instead report a more nuanced decision-making calculus influenced by the advice of physicians,⁷² family pressures,⁷³ and the potential for financial benefit.⁷⁴ However, when the data are stratified by the severity of the subject's disease, the binary picture reappears.⁷⁵ While altruism may strongly motivate the decisions of healthy research subjects,⁷⁶ studies investigating participants in Phase I cancer trials – the majority of whom are terminally ill – consistently identify therapeutic benefit as the primary motive for participation.⁷⁷

This finding validates the concern that creation of a market for unapproved drugs will negatively impact the clinical trial process. If patients, upon the advice of their physician, can simply purchase an experimental therapy, it is likely that many will do so. Clinical trial enrollment involves both hassle (in the form of screening procedures required to assess eligibility) and risk (in placebo-controlled trials, the patient may not receive the active drug) that terminally ill patients may be unwilling to contemplate. This factor, therefore, lends support to the government's argument that its interest in restricting access to unapproved drugs is a compelling one.

3. Will a Market Exist?

The weight of the FDA's interest in preserving the current clinical trial system depends upon the actions of the pharmaceutical industry. Assuming that a constitutional right to access post-Phase I drugs does not give rise to a concomitant obligation to provide them, pharmaceutical companies will have a choice whether to make their products available to terminally ill consumers. If the companies choose not to, then clinical trials will retain their near-monopoly over the distribution of unapproved drugs. This would undercut the second prong of the FDA's asserted

⁷²C.K. Daugherty et al., *Perceptions of Cancer Patients and Their Physicians Involved in Phase I Trials*, 13 J. CLINICAL ONCOLOGY 1062, 1064 (1995).

⁷³Kathleen M. Schutta & Caroline B. Burnett, *Factors that Influence a Patient's Decision to Participate in a Phase I Cancer Clinical Trial*, 27 ONCOLOGY NURSING FORUM 1435, 1437 (2000).

⁷⁴J.P. Bentley & P.G. Thacker, *The Influence of Risk and Payment on the Research Participation Decision Making Process*, 30 J. MED. ETHICS 293, 296-97 (2004).

⁷⁵Monica H. Schaeffer et al., *The Impact of Disease Severity on the Informed Consent Process in Clinical Research*, 100 AM. J. MED. 261, 266 (1996); Franklin G. Miller & Donald L. Rosenstein, *The Therapeutic Orientation to Clinical Trials*, 348 NEW ENG. J. MED. 1383, 1383-86 (2003).

⁷⁶See C. Rabin & N. Tabak, *Healthy Participants in Phase I Clinical Trials: The Quality of Their Decision to Take Part*, 15 J. CLINICAL NURSING 971 (2006).

⁷⁷See Schutta & Burnett, *supra* note 73; Daugherty et al., *supra* note 72; Z.A. Nurgat et al., *Patient Motivations Surrounding Participation in Phase I and Phase II Clinical Trials of Cancer Chemotherapy*, 92 BRIT. J. CANCER 1001 (2005).

interest, significantly weakening the agency's justification for regulation.

There are several financial and logistical concerns that militate against widespread industry participation in a post-Phase I market. Most significantly, there often is a limited drug supply in the early stages of development. The batches prepared for early drug studies are usually small because making larger amounts available is expensive and not considered reasonable until there is evidence that the drug is of therapeutic (and therefore financial) value.⁷⁸ The new market created by the *Abigail Alliance* decision is unlikely to change this cost-benefit analysis. Because the constitutional right recognized by the court requires (1) terminal illness, (2) mental competence, (3) a cooperating physician, and (4) no alternative means of access, the pool of eligible patient-consumers is likely to be quite small.⁷⁹ Thus, the economies of scale needed to prompt manufacturers to produce larger quantities of drugs simply may not exist.

One might argue that past participation in other expanded access programs indicates that pharmaceutical companies will sell their products to patients seeking to exercise the *Abigail Alliance* right. For example, eight years after Treatment INDs were first made available, thirty-four manufacturer applications had been granted by the FDA.⁸⁰ However, Treatment INDs (as well as other expanded access mechanisms) are normally granted for drugs already in Phase III testing, at which point companies have made the decision to scale up their manufacturing processes.⁸¹ Thus, willingness to participate in expanded access programs can be seen as a function of the very different cost-benefit analysis that occurs at this later stage of testing, and does not necessarily predict similar behavior earlier in the drug approval process.

There may also be competition for internal resources between expanded access and the regulatory programs that lead to drug approval. For example, "[t]he process of individualized packing and shipping of drugs for single patient use on an emergent basis can be very disruptive to departments that are organized to pack and ship drugs in a scheduled manner for clinical trials."⁸² Because the market for an approved drug often offers far greater financial incentives than the market for post-Phase I drugs, companies may be unwilling to divert resources from the approval process to satisfy the demands of this smaller market.

Finally, the use of an investigational drug in an uncontrolled setting in patients

⁷⁸Tom Class, *Expanded Access to Unapproved Medical Products: Compassionate Use*, REG. AFF. FOCUS MAG., May 2006, available at http://www.raps.org/s_raps/refocus_article.asp?TRACKID=&CID=618DID=27208.

⁷⁹*Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*, 445 F.3d 470 (D.C. Cir. 2006).

⁸⁰Edward L. Korwek, *Human Biological Drug Regulation: Past, Present, and Beyond the Year 2000*, 50 FOOD & DRUG L.J. 123, 137 (1995).

⁸¹Lois K. Perrin, Note, *The Catch-22 for Persons with AIDS: To Have or Not to Have Easy Access to Experimental Therapies and Early Approval for New Drugs* 69 S. CAL. L. REV. 105, 141 (1995).

⁸²*Compassionate Use of Investigational New Drugs: Is the Current Process Effective?* Hearing Before the H. Comm. on Government Reform, 107th Cong. (2001) (statement of Robert J. Temple, Associate Director for Medical Policy, Center for Drug Evaluation and Research, Food and Drug Administration).

with very advanced disease, could lead to adverse reactions that might raise difficult but spurious safety and efficacy concerns about the drug. This is evident by the fact that “[t]he FDA expects very low response rates . . . [and numerous adverse events in clinical trial participants] who have received multiple previous therapies.”⁸³ Such outcomes do not necessarily damage a drug’s chance for approval, because sophisticated statistical analyses are used to segregate the drug’s effects from those associated with the patient’s underlying illness.⁸⁴ However, adverse events occurring outside of the clinical trial context are not subject to the same rigorous monitoring requirements and, thus, cannot be analyzed in this way. This introduces an element of uncertainty into the drug development process, which could reduce a product’s chances for approval.

These logistical barriers, together with limited financial incentives, suggest that pharmaceutical companies are unlikely to participate in a market for post-Phase I drugs. This conclusion further damages the FDA’s asserted interest in regulation, which assumes that patients would abandon clinical trials should a market exist for procuring unapproved medications. If no market were to exist, this assumption would be unfounded.

IV. CONCLUSION

FDA regulation undoubtedly serves to promote compelling government interests in consumer protection and public health. However, in questioning whether these interests support restrictions on access to post-Phase I drugs by terminally ill patients, the Court of Appeals for the D.C. Circuit suggested that the answer is no:

In this case, the government’s interest may prove to be weaker than that acknowledged by the United States Supreme Court in *United States v. Rutherford* because the Alliance seeks only access to investigational new drugs that the FDA, after Phase I human trials, has deemed sufficiently safe for human testing on a substantial number of human beings. In other words, the Alliance seeks for its members the same right of access enjoyed by those terminally ill patients lucky enough to secure a spot in Phase II trials.⁸⁵

Building upon the court’s logic, this article argues that restrictions on terminally ill patients’ access to post-Phase I drugs do not further a compelling government interest. Such restrictions provide no affirmative benefits for these patients, nor do they offer meaningful protection from self-induced harm. While restricting access to unapproved drugs does benefit the public at large, that benefit is not threatened by the narrow exception required by the *Abigail Alliance* decision. Consequently, FDA regulation of unapproved drugs must be modified to overcome this constitutional infirmity.

⁸³*Id.*

⁸⁴*Id.*

⁸⁵*Abigail Alliance for Better Access to Developmental Drugs v. Von Echenbach*, 445 F.3d 470, 486 (D.C. Cir. 2006).