Winter 2009

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Patricia J. Zettler
Georgia State University College of Law, pzettler@gsu.edu

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THE IMPLICATIONS OF POST-PHASE 1 AND "OFF-LABEL" TREATMENT USE OF EXPERIMENTAL DRUGS: HOW EXPANSIVE SHOULD EXPANDED ACCESS BE?

Patricia J. Zettler*

In 1999, nineteen-year-old Abigail Burroughs was diagnosed with cancer of the head and neck.\(^1\) Abigail underwent radiation and chemotherapy, but these conventional treatments were unsuccessful.\(^2\) Her oncologist informed Abigail and her family of two experimental drugs, gefitinib and cetuximab, that were beginning Phase 2 clinical trials in the Food and Drug Administration (FDA) approval process.\(^3\) The oncologist believed these experimental drugs might be an effective treatment option for her because the drugs were designed to target epidermal growth factor receptors, which were highly expressed in her tumor.\(^4\) Abigail's family sought to enroll her in the Phase 2 clinical trials, but she was unable to participate in the trials because she did not meet the inclusion criteria for the clinical trials of either drug.\(^5\) Abigail and her family then unsuccessfully sought access to these drugs outside of the clinical trials through the FDA's expanded access programs, even though the drugs were being studied only for use in colon cancer, not head and neck cancer.

Approximately two years after Abigail's diagnosis, and seven months after Abigail and her family began their quest to obtain these experimental drugs, Abigail died at twenty-one years of age.\(^6\) Following her death, her father, Frank Burroughs, founded the non-profit advocacy organization, *J.D. Candidate 2009, Stanford Law School. I would like to thank Professor Hank Greely for his insightful comments and generous feedback on this Note. I am also grateful to my brother, Jeffrey Zettler, for his suggestions and expert copy-editing.

5. Jacobson & Parmet, supra note 1, at 205.
Abigail Alliance for Better Access to Developmental Drugs (Abigail Alliance), to create greater access to experimental drugs for terminally ill patients.\(^7\) To achieve this goal, Abigail Alliance filed a Citizen Petition with the FDA and then filed a lawsuit against the FDA in 2003.\(^8\)

Abigail Alliance is not the only organization that has tried to expand terminally ill patients’ access to investigational drugs. Cancer patients first lobbied for expanded access in the 1970s. In the 1980s and 1990s, HIV/AIDS patients successfully fought for regulations that formalized expanded access programs.\(^9\) Each of these challenges to the restrictions on access imposed by the FDA approval process raised legal, ethical, and policy questions regarding the FDA approval process and terminally ill patients’ right to access investigational drugs. The Abigail Alliance case, however, posed new questions. Abigail Burroughs sought drugs earlier in the clinical trials process (after only Phase 1 trials were completed) and sought drugs that were going through the approval process for a condition she did not have (colon cancer).

This Note evaluates the issues raised by expanded access to post-Phase 1 drugs and to drugs intended for a different condition than the patients’ particular disease (off-label access), and it concludes that such access may not strike the appropriate balance between safety and early availability of effective treatments for terminal illnesses. Part I of this Note provides an overview of the current process by which the FDA regulates the safety and effectiveness of drugs.\(^10\) In Part II, this Note examines the history of expanded access programs, the current options, and the operation of those options. Part III discusses Abigail Alliance’s lawsuit against the FDA and concludes the D.C. Circuit appropriately held that terminally ill patients do not have a constitutional right to access investigational drugs and the courts may not be the appropriate venue for making policy determinations about expanded access. In Part IV, the Note examines the policy proposals of both Abigail Alliance and the FDA to change the expanded access options. Part V analyzes the policy implications of allowing post-Phase 1 and off-label access. The Note concludes that the FDA’s own policy proposal, which clarifies the current system, strikes the best balance of the proposals and recommends that FDA consider developing better methods for communicating with stakeholders about expanded access programs.

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7. Id.
9. See, e.g., PHILIP J. HILTS, PROTECTING AMERICA’S HEALTH: THE FDA, BUSINESS, AND ONE HUNDRED YEARS OF REGULATION 161-65 (2003) (describing cancer patients’ advocacy); Okie, supra note 4, at 438 (providing a timeline of access rights); Jerome Groopman, The Right to a Trial: Should Dying Patients Have Access to Experimental Drugs?, THE NEW YORKER, Dec. 18, 2006, at 40, 43 (describing HIV/AIDS patients’ advocacy). In the 1980s, there was even a made-for-TV movie about a father’s attempt to obtain an experimental drug to treat his daughter’s severe epilepsy. See John Corry, Fight for Life on ABC, N.Y. TIMES, Mar. 23, 1987, at C18.
10. Although the FDA regulates products other than drugs, such as food, biologics, and medical devices, this Note will focus only on the drug approval process.
I. OVERVIEW OF DRUG REGULATION

A. The History of Drug Regulation

Before a drug can be marketed and distributed in the United States, it must receive approval from the FDA. Modern drug regulation began in the early twentieth century and has evolved over the past one hundred years. In 1906, Congress passed the Pure Food and Drugs Act. The Act required accurate labeling of drugs but did not regulate the safety or effectiveness of those drugs.\(^{11}\) In 1938, following the death of 107 people who ingested the liquid form of sulfanilamide,\(^{12}\) Congress enacted the Federal Food, Drug and Cosmetic Act (FDCA).\(^{13}\) For the first time, the FDCA required pharmaceutical companies to prove the safety of their drugs to the FDA before marketing those drugs.\(^{14}\) Although the FDA began to develop standards for demonstrating both the safety and effectiveness of specific drugs,\(^{15}\) the FDA did not have formal standards for assessing the effectiveness of all new drugs for the next two and one-half decades.\(^{16}\) Pharmaceutical companies routinely tested investigational drugs by simply sending them to physicians to give to their patients.\(^{17}\)

The current form of stricter FDA drug regulation began in 1962\(^{18}\) after a narrowly averted disaster related to thalidomide—a drug approved outside the U.S. for use as a sedative and to ease nausea during pregnancy.\(^{19}\) A company wanting to market thalidomide in the U.S. distributed 2.5 million tablets of the drug to 1,267 physicians, who then gave the drug to approximately 20,000 patients for experimental use.\(^{20}\) Even though the company followed the standard testing procedure of the time, Dr. Frances Kelsey, one of the physician drug reviewers at the FDA, refused to approve thalidomide for use in

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\(^{12}\) Sulfanilamide was a drug used to treat streptococcal infections (e.g., strep throat) and was traditionally taken in pill or powder form. In response to customer demand for a liquid form, the manufacturer discovered that the drug could be made into a sweet-tasting liquid by dissolving it in diethylene glycol. Unfortunately, the manufacturer did not test the elixir for toxicity prior to shipping. Diethylene glycol is typically used as antifreeze and can cause kidney failure if ingested. See id; Carol Ballentine, U.S. Food & Drug Administration, Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanamide Incident, FDA CONSUMER MAG., Jun. 1981, available at http://www.fda.gov/oc/history/elixir.html.

\(^{13}\) Wax, supra note 11, at 459.

\(^{14}\) See id.

\(^{15}\) See U.S. Food & Drug Administration, Milestones in U.S. Food & Drug Law, http://www.fda.gov/opacom/backgrounders/miles.html (last visited Nov. 3, 2008). For example, in 1941, Congress passed the “Insulin Amendment,” which required the FDA “to certify the purity and potency” of insulin. Id. Similarly, in 1945, Congress passed the “Penicillin Amendment,” requiring the FDA to test the safety and effectiveness of all penicillin products, and later all antibiotics. Id.

\(^{16}\) See HILTS, supra note 9, at 150-51.

\(^{17}\) Id. at 150; Groopman, supra note 9, at 42.

\(^{18}\) See HILTS, supra note 9, at 161-65.

\(^{19}\) Groopman, supra note 9, at 42.

\(^{20}\) HILTS, supra note 9, at 150-51.
the United States without more rigorous clinical trials. Thalidomide was later found to cause severe birth defects, including deformed limbs, closed ear canals, and malformed intestines, in the infants whose mothers took the drug. Approximately forty cases of severe birth defects occurred in the United States. But if thalidomide had been approved for marketing in the U.S., an estimated ten thousand infants would have suffered birth defects. In 1962, after thalidomide's side effects were made public, Congress passed the Kefauver-Harris amendments to the FDCA that gave the FDA greater power and required pharmaceutical companies to demonstrate both the safety and effectiveness of their products through "adequate and well-controlled investigations" to obtain marketing approval.

B. Phases of Clinical Trials

In the current approval process, a new drug is first studied in animals during "preclinical" trials. If the drug shows promise in the preclinical trials, the drug sponsor (usually a pharmaceutical company, academic research center, or other research entity) submits an Investigational New Drug Application (IND) to the FDA. The FDA reviews INDs for safety, scientific quality of the proposed clinical trials, and plausibility of eventual approval.

If the FDA approves an IND, clinical trials may begin. The investigational drug must be studied in three sequential phases of clinical trials before the FDA will approve an investigational drug for marketing and distribution. This clinical investigation is lengthy; a new drug typically reaches the market seven to eight years after the start of clinical trials.

21. See id. at 152-65; Groopman, supra note 9, at 42.
22. Groopman, supra note 9, at 42.
23. HILTS, supra note 9, at 158.
24. Id. In Germany and several other European countries where thalidomide had been approved, there were approximately 8,000 cases of severe birth defects and an estimated 5,000 to 7,000 in-utero fetal deaths due to thalidomide.
25. Drug Amendments of 1962, Pub. L. No. 87-781, § 102, 76 Stat. 780, 781. See also HILTS, supra note 9 at 161-65 (explaining the impact of the thalidomide incident on Congress' passing of the Amendments); Okie, supra note 4, at 438; Groopman, supra note 9, at 42.
27. Id. (explaining that a drug must show promise in preclinical trials). See also 21 C.F.R. § 312.23 (2007) (describing the IND requirements).
1. Phase 1

A Phase 1 study of an investigational drug involves twenty to eighty human volunteers and is the first introduction of the drug into humans.\(^{31}\) The purpose of a Phase 1 study is "to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness," and to obtain "sufficient information about the drug's pharmacokinetics and pharmacological effects... to permit the design of well-controlled, scientifically valid, Phase 2 studies."\(^{32}\)

For a typical drug, Phase 1 lasts a mean of 21.6 months.\(^{33}\) At most, twenty-two percent of the drugs that enter Phase 1 clinical trials are eventually approved.\(^{34}\) This approval rate varies depending on the target illness. One study found that approximately twenty percent of investigational drugs intended to treat cardiovascular diseases that enter clinical trials are eventually approved, while only five percent of drugs intended to treat cancer are eventually approved.\(^{35}\)

Unlike Phase 2 and Phase 3 studies, most Phase 1 studies are conducted with healthy volunteers.\(^{36}\) In other words, Phase 1 research participants typically do not have the condition that the investigational drug is intended to treat. The FDA permits only investigational drugs that are both targeted to life-threatening illnesses and likely to produce serious side effects to be studied in persons with the indicated condition at the Phase 1 level.\(^{37}\)

2. Phase 2

If Phase 1 studies indicate that the investigational drug is sufficiently safe

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\(^{32}\) Id.


\(^{34}\) Joseph A. DiMasi, Risks in New Drug Development: Approval Success Rates for Investigational Drugs, 69 CLINICAL PHARMACOLOGY & THERAPEUTICS 297, 303 fig.7 (2001) [hereinafter DiMasi, Risks]. This is one of the highest estimates of drug approval rates; the actual percentage may be lower. See INSTITUTE OF MEDICINE, THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC 37 (2007) [hereinafter FUTURE OF DRUG SAFETY]; Ismail Kola & John Landis, Can the Pharmaceutical Industry Reduce Attrition Rates?, 3 NATURE REV. DRUG DISCOVERY 711, 711 (2004) (finding that only eleven percent of investigational drugs that enter clinical trials are eventually approved by the FDA or the European regulatory bodies).

\(^{35}\) Kola & Landis, supra note 34, at 712.


\(^{37}\) Id.
for further study, Phase 2 clinical trials of the drug are conducted. Phase 2 trials are conducted with a "small number" of human volunteers, usually "no more than several hundred." The purpose of a Phase 2 study is to "evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug." To this end, Phase 2 trials usually have both a control and an intervention group. Participants in the control group are given a placebo or the standard therapy for their illness, while participants in the intervention group receive the investigational drug. Participants are randomly assigned to either the control or intervention groups and usually do not know to which group they have been assigned. Approximately thirty-three percent of the drugs entering Phase 2, like the drugs Abigail Burroughs and her family sought to access, are eventually approved. Phase 2 clinical trials last a mean of 25.7 months.

3. Phase 3

If Phase 2 trials demonstrate sufficient evidence of effectiveness and no major safety concerns, Phase 3 trials begin. Phase 3 involves the largest number of human subjects; the studies are conducted with several hundred to several thousand human volunteers. Like Phase 2 trials, Phase 3 trials are usually designed to have both a control and an intervention group. They "are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling." Approximately seventy-nine percent of drugs that enter Phase 3 clinical trials are eventually approved. Phase 3 clinical trials last a mean of 30.5 months.

38. FDA's Drug Review Process, supra note 26 ("Phase 2 studies begin if Phase 1 studies don't reveal unacceptable toxicity.").
39. 21 C.F.R. § 312.21(b) (2007).
40. Id.
41. See Rados, supra note 36.
42. See id. (In some cases, the control group receives the standard therapy, and the intervention group receives the standard therapy plus the investigational drug.).
43. See id.
44. See DiMasi, Risks, supra note 34, at 303 fig.7.
45. DiMasi et al., Price of Innovation, supra note 30, at 165 fig.3.
47. 21 C.F.R. § 312.21(c) (2007).
48. See Rados, supra note 36. Phase 3 trials also often have several intervention groups that each receive different amounts of the investigational drug so that dosing regimens can be evaluated. The different dosing regimens are intended to provide the information needed for "physician labeling." See 21 C.F.R. § 312.23(a)(6)(iii)(e) (requiring that INDs describe the method for determining the appropriate dose); Linda Bren, The Advancement of Controlled Clinical Trials, FDA CONSUMER MAG., Mar.-Apr. 2007, available at http://www.fda.gov/fdac/features/2007/207_trials.html (explaining why the FDA requires dosing investigation).
49. 21 C.F.R. § 312.21(c) (2007).
50. See DiMasi, Risks, supra note 34, at 303 fig.7.
4. Post-Phase 3

If Phase 3 trials indicate that the investigational drug is safe and effective for patients with the targeted illness, the sponsor submits a New Drug Application (NDA) to the FDA. In many cases, the sponsor also agrees to conduct post-marketing studies, called Phase 4 trials, so that the FDA can collect additional data regarding the drug’s safety, effectiveness, and optimal use. Typically, a drug intended to treat a serious illness is approved about one year after the NDA is submitted. Approximately eighty-five percent of NDAs are approved.

C. “Off-Label” Use

“Off-label” use refers to any situation in which a patient uses an approved drug in a way that differs from the instructions on the FDA-approved drug label. The FDA approves drugs for the specific indications studied in the clinical trials process and allows marketing for those purposes. Accordingly, the required label for the drug pertains only to that specific purpose. In other words, off-label use occurs when a patient uses the drug for a condition or in a manner that was not studied during the clinical trial process.

A physician may prescribe a drug for an off-label use, or a patient independently may choose to use a drug in a manner different from the instructions on the label (e.g., taking a higher dose of a drug than is recommended on the label). This Note focuses on off-label prescriptions because, although the FDA could theoretically prohibit patient-initiated off-label use, such a ban would be impracticable. Once a patient has a prescription drug, monitoring the use of that drug is virtually impossible.
The FDA cannot prohibit off-label prescriptions because the scope of the FDA’s authority “extends to manufacturers of drugs but not to the physicians who dispense them.”62 Off-label prescribing is common, although the frequency differs among functional classes of drugs.63 Some off-label prescribing practices are scientifically justified and beneficial.64 One off-label success story is Prozac, which was originally approved as an appetite suppressant, but has proven to be an effective anti-depressant.65 Fenfluramine and phentermine, on the other hand, were both approved separately as weight loss drugs but were sometimes prescribed in an off-label two-drug combination, known as fen-phen.66 In combination, the two drugs caused damage to heart valves, and both were eventually removed from the market.67

II. ACCESS TO INVESTIGATIONAL DRUGS OUTSIDE OF CLINICAL TRIALS

A. History of Access Litigation and Activism

For much of the FDA’s history, no formal regulations granted terminally ill patients access to investigational drugs outside of clinical trials.68 Terminally ill patients were able to receive investigational drugs only through an informal compassionate use exemption that the FDA granted on a case-by-case basis. In order to get such an exemption, a patient’s physician had to be willing to request the exemption from the FDA, and the drug manufacturer had to be willing to provide the drug to the patient free of charge.69 Terminally ill patients’ litigation and political activism led the FDA to create formal options granting access to investigational drugs outside of clinical trials.

1. United States v. Rutherford

In 1975, cancer patients launched the first major attempt to gain access to an unapproved drug outside of clinical trials by filing a class action lawsuit to enjoin the FDA from interfering with the interstate sale and shipment of laetrile, a drug not approved by the FDA.70 The lead plaintiff, Glen L.

62. See id. at 190; see also CECCOLI, supra note 56, at 158 (“[T]he FDA does not regulate the practice of medicine.”).
63. See Radley, supra note 56, at 1025.
64. See CECCOLI, supra note 56, at 157-58; Radley, supra note 56, at 1025.
65. CECCOLI, supra note 56, at 158.
66. Id. at 159.
67. Id.
70. See United States v. Rutherford, 442 U.S. 544, 548 (1979). See also, Okie, supra note 4, at 438 (identifying Rutherford as the first major attempt at access outside of clinical trials for the terminally ill). Laetrile is a compound found in some fruits, nuts and other plants. Some believe it is an effective alternative treatment for cancer; however, clinical studies of laetrile in humans and animals have shown little effectiveness in treating cancer, and it is not approved for cancer treatment in the U.S. See, e.g., National Cancer Institute, Laetrile/Amygdalin, http://www.cancer.gov/cancertopics/pdq/cam/laetrile (last visited Nov. 5, 2008). Laetrile
Rutherford, was diagnosed with colorectal cancer in 1971. Fearful of the standard surgical treatment, Mr. Rutherford did not show up for his scheduled operation; instead, he saw a physician in Mexico who gave him laetrile. Mr. Rutherford believed that the laetrile cured his cancer and that he needed to continue taking it to remain healthy.\textsuperscript{71}

The district court\textsuperscript{72} held FDA regulation of laetrile was improper based on a statutory grandfather provision prohibiting regulation of drugs on the market before 1962. In the alternative, the district court held that the regulation infringed on the constitutional right to privacy, which included the right to determine one's own individual health care plan.\textsuperscript{73} The Tenth Circuit did not reach the statutory or the constitutional issues but upheld the district court's decision because "the 'safety' and 'effectiveness' terms used in the [FDCA] have no reasonable application to terminally ill cancer patients."\textsuperscript{74}

Relying on congressional intent, agency deference, and the plain language of the FDCA, the Supreme Court reversed the Tenth Circuit's decision.\textsuperscript{75} First, the Supreme Court reasoned that when Congress passed the FDCA in 1938 and the Kefauver-Harris amendments in 1962, Congress intended to protect terminally ill patients from "fraudulent cures."\textsuperscript{76} Second, the Court noted that "[i]n implementing the statutory scheme, the FDA has never made exceptions for drugs used by the terminally ill,"\textsuperscript{77} and the FDA's longstanding interpretation of the FDCA was "entitled to substantial deference."\textsuperscript{78} Third, the plain language of the FDCA contained no exceptions for drugs intended to treat terminal illnesses.\textsuperscript{79} The Court also found that ensuring drug safety and effectiveness might be particularly important for those drugs intended to treat presented a different situation than the Abigail Alliance case because it was not actually undergoing clinical investigation. \textit{Rutherford}, 442 U.S. at 550-51. The laetrile litigation is relevant to the current questions of expanded access, however, because later courts cite to \textit{Rutherford} and because the litigation marked patients’ first major attempt to circumvent the FDA approval process.


\textsuperscript{72} The District Court's decision followed a remand to the FDA to determine whether laetrile was in fact a "new drug." \textit{Rutherford} v. United States, 542 F.2d 1137, 1143 (10th Cir. 1976) (remanding the case to the FDA to develop the record).

\textsuperscript{73} See \textit{Rutherford} v. United States, 438 F. Supp. 1287, 1294, 1298-99, 1301 (W.D. Okla. 1977). Specifically, the District Court found that laetrile was exempt from the FDA's "test of general recognition by experts as being both safe and effective for its claimed uses," \textit{id.} at 1294, because "[e]xtensive use of the substance, its commercial availability, and its recognition as being safe, all previous to 1962, are well-documented in the record." \textit{Id.} at 1296. Regarding the constitutional right, the District Court held that laetrile was nontoxic, and denying cancer patients the freedom to choose a nontoxic course of treatment, whether that treatment was effective or not, infringed the patients' constitutional privacy interest and was not in furtherance of a compelling state interest. \textit{Id.} at 1298-99.

\textsuperscript{74} \textit{Rutherford} v. United States, 582 F.2d 1234, 1236 (10th Cir. 1978).

\textsuperscript{75} See \textit{Rutherford}, 442 U.S. at 552-53.

\textsuperscript{76} \textit{Id.}

\textsuperscript{77} \textit{Id.} at 553.

\textsuperscript{78} \textit{Id.}

\textsuperscript{79} See \textit{id.} at 555.
life-threatening illnesses:

An otherwise harmless drug can be dangerous to any patient if it does not produce its purported therapeutic effect. But 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. . . . Thus, as the Commissioner concluded, to exempt from the Act drugs with no proved effectiveness in the treatment of cancer would lead to needless deaths and suffering among . . . patients characterized as terminal who could actually be helped by legitimate therapy. 80

Thus, in Rutherford, the Supreme Court affirmed the FDA’s power to regulate new drugs intended to treat terminal illnesses and emphasized the importance of marketing only safe and effective drugs to terminally ill patients. On remand, the Tenth Circuit rejected the district court’s finding that the FDA regulation infringed on a constitutional right of privacy. 81 Following Rutherford, several similar cases were litigated in federal and state courts with the same result; the courts found no fundamental right for patients to access or for sponsors to sell unapproved investigational drugs. 82

2. The HIV/AIDS epidemic

After Rutherford, the FDA did not promulgate any express rules for granting terminally ill patients access to investigational drugs outside of clinical trials 83 until the onset of the AIDS epidemic in the 1980s. 84 In 1981, the first reports of AIDS were published in medical literature. 85 By 1989, there

80. Id. at 556-57 (citations and internal quotations omitted).
81. See Rutherford v. United States, 616 F.2d 455, 457 (10th Cir. 1980).
82. See Carnohan v. United States, 616 F.2d 1120, 1122 (9th Cir. 1980) (finding no fundamental right to use laetrile, based on Rutherford); Cowan v. United States, 5 F.Supp.2d 1235, 1243 (N.D. Okla. 1998) (concluding that a person living with AIDS had no right to access an unapproved treatment, particularly when the person had not applied for treatment use under the FDA’s expanded access programs); People v Privitera, 23 Cal.3d 697, 701 (Cal. 1979) (finding no fundamental right to sell laetrile); Seely v. State, 132 Wash.2d 776, 792 (1997) (no fundamental right to use marijuana as a medical treatment to counteract the effects of chemotherapy). See also Gonzales v. Raich, 545 U.S. 1, 28 (2005) (citing Rutherford, 442 U.S. at 544) (“the dispensing of new drugs, even when doctors approve their use, must await federal approval”); Alissa Puckett, Comment: The Proper Focus for FDA Regulations: Why the Fundamental Right to Self-Preservation Should Allow Terminally Ill Patients with No Treatment Options to Attempt to Save Their Lives, 60 SMU L. REV. 635, 645-51 (2007) (discussing all of these cases in more depth). The D.C. Circuit panel’s decision in Abigail Alliance, discussed in Part IV, represents the only significant departure from these holdings. Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach, 445 F.3d 470 (D.C. Cir. 2006), vacated en banc, 495 F.3d 695 (D.C. Cir. 2007).
83. The FDA did, however, create an informal “personal use import exemption” that allowed certain patients to import small quantities of unapproved drugs for their own individual medical use. See Greenberg, supra note 69, at 316-17.
84. Groopman, supra note 9, at 42.
were over one hundred thousand reported cases of HIV/AIDS in the U.S.\textsuperscript{86} and only one approved treatment, AZT.\textsuperscript{87} In the context of the rapid spread of the disease, the high mortality, the lack of effective treatment options, and the social stigma associated with the disease, HIV/AIDS patients became politically active in an attempt to force an unwilling presidential administration to address their medical needs.\textsuperscript{88} Faced with this political pressure, the FDA created the treatment IND program in 1987.\textsuperscript{89} The program allows patients ineligible for clinical trials to obtain investigational drugs that have completed at least Phase 2 clinical trials.\textsuperscript{90}

\section*{B. Current Expanded Access Options}

Since 1987, the FDA has created a variety of mechanisms to address terminally ill patients' desire to gain treatment access to experimental drugs during the clinical trial process.\textsuperscript{91}

1. Treatment IND Program

The treatment IND program was the first, and is the most widely known, formal option for accessing investigation drugs outside of clinical trials. It provides access for groups of terminally ill patients, rather than access for single patients on a case-by-case basis.\textsuperscript{92} The purpose of the treatment IND


\textit{See} Centers for Disease Control, HIV/AIDS SURVEILLANCE REP., Jan. 1990, at 1, 6, \textit{available at} http://www.cdc.gov/hiv/topics/surveillance/resources/reports/past.htm#surveillance (providing number of AIDS cases); OSMOND, \textit{supra} note 85 (indicating AZT was approved in 1987 and was the only effective treatment in the 1980s).\textsuperscript{87}

\textit{Id.} at 246-50.\textsuperscript{88}

\textit{See id.} at 247; Groopman, \textit{supra} note 9, at 42.\textsuperscript{90}

\textit{See} 21 C.F.R. § 312.34(a) (2007); HILTS, \textit{supra} note 9, at 247 (describing the context in which the FDA created the treatment IND program). Patients could obtain the INDs either on a case-by-case basis from their own physicians, or as part of a more general "expanded-access program." HILTS, \textit{supra} note 9, at 247.\textsuperscript{91}

\textit{See}, e.g., U.S. National Library of Medicine, National Institutes of Health, \textit{FAQ: ClinicalTrials.gov} – What is an Expanded Access Protocol?, http://www.nlm.nih.gov/services/etexpaccess.html (last visited Nov. 28, 2008) (explaining that persons who do not meet the criteria to enter into clinical trials may be eligible to receive an experimental drug through an expanded access program.). The FDA also has expedited review mechanisms in place to help accelerate the approval process for investigational drugs targeted to terminal and serious illnesses. \textit{See} 21 C.F.R. § 312.80. These programs are beyond the scope of this paper because this paper focuses on access to unapproved investigational drugs, whereas expedited approval programs focus on hastening the approval process and patients' access to approved drugs.\textsuperscript{92}

program is "to facilitate the availability of promising new drugs to desperately ill patients as early in the drug development process as possible, before general marketing begins, and to obtain additional data on the drug's safety and effectiveness." 93

An investigational drug may be made available outside of clinical trials only to treat either "serious" 94 or "immediately life-threatening" 95 diseases. For serious illnesses, treatment use is usually permitted during Phase 3 clinical trials "or after all clinical trials have been completed." 96 Only "in appropriate circumstances" will treatment use for a serious disease be permitted during Phase 2 trials. 97 For an immediately life-threatening disease, "a drug may be made available for treatment use under this section earlier than Phase 3 but ordinarily not earlier than Phase 2." 98 In practice, the FDA usually does not allow post-Phase 1 access, the stage at which Abigail Burroughs requested access, through the treatment program. 99

The regulation further stipulates that the FDA "shall permit" treatment use of an investigational drug if three other specific criteria are met. 100 First, there must be no "comparable or satisfactory alternative drug or therapy" to treat the stage of the particular disease for which treatment use is sought. 101 Second, the drug must be under investigation in a controlled clinical trial as part of an IND application or it must have completed clinical trials. 102 Finally, the sponsor of the drug must be "actively pursuing marketing of the investigational drug with due diligence." 103

Even if all of these criteria are met, the FDA may deny requests for treatment use in certain circumstances. 104 For a serious disease, the FDA may

93. 21 C.F.R. § 312.34(a) (2008). See also 21 U.S.C. § 360bbb(c) (2007) (authorizing the FDA to create the treatment program). In addition to authorizing the treatment program, 21 U.S.C. § 360bbb(c) authorizes the Secretary of the Department of Health and Human Services to inform relevant health associations of expanded access programs, so that physicians and their patients are aware of investigational drugs that might be used for treatment.

94. The regulation does not define what constitutes a "serious" disease. See 21 C.F.R. §§ 312.3, 312.34.

95. An "immediately life-threatening" illness is "a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment." Id. § 312.34(b)(3)(ii).

96. Id. § 312.34(a).

97. Id.

98. Id.

99. See, e.g., Okie, supra note 4, at 439 (stating that drugs made available to patients outside of clinical trials usually are in Phase 3 trials); U.S. Food and Drug Administration, Expanded Access and Expedited Approval of New Therapies Related to HIV/AIDS, http://www.fda.gov/oashi/aids/expanded.html (last visited Jan. 2, 2009) (explaining that for HIV/AIDS drugs treatment INDs are usually granted "well into clinical trials, or when clinical trials have been completed") [hereinafter Expanded Access].

100. 21 C.F.R. § 312.34(b)(1).

101. Id. § 312.34(b)(1)(i).

102. Id. § 312.34(b)(1)(ii).

103. Id. § 312.34(b)(1)(iii).

104. Id. § 312.34(b)(2)-(3).
deny a request "if there is insufficient evidence of safety and effectiveness to support such use." 105 For immediately life-threatening diseases, the FDA may deny treatment use if:

... the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug: (A) May be effective for its intended use in its intended patient population; or (B) Would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury. 106

Notably, the treatment use regulation does not address whether patients can obtain off-label access to investigational drugs. 107

Only the drug sponsor or a licensed practitioner, not a terminally ill patient, may apply for treatment use. 108 Licensed practitioners, moreover, may apply only if the sponsor refuses to apply. 109 In most circumstances, these restrictions on who may apply might be a formality. Sponsors and physicians are likely to have the expertise to supply the FDA with the information necessary to gain approval for treatment use, such as the rationale for using an investigational drug for a particular group of patients. 110 Patients learn about drugs in the approval process in a variety of ways. Some patients may not be aware of such drugs unless their physician informs them. Other patients might learn independently of investigational drugs through advertisements for clinical trials or advocacy groups. 111 Patient advocacy groups, such as Abigail Alliance, might be knowledgeable about unapproved drugs in the pipeline and the science behind their development. However, the FDA does not have the authority to require a sponsor to provide treatment use. 112 Thus, even in circumstances when a patient independently learns of an investigational drug, the FDA restrictions on who may apply are not likely to be the obstacle for patients.

Finally, sponsors are permitted to charge patients for treatment use of an unapproved drug, provided:

(i) There is adequate enrollment in the ongoing clinical investigations

105. Id. § 312.34(b)(2).
106. Id. § 312.34(b)(3).
107. See id. § 312.34 (failing to address patient access to off-label drugs).
108. See id. § 312.35(a)-(b).
109. See id. § 312.35(b)(1).
110. See id. §312.35(a)(1)(ii).
111. See, e.g., Rados, supra note 36 (noting that patients often learn of clinical trials from newspapers and the NIH clinical trials website).
112. See 21 C.F.R. § 312.34 (providing no authority to require that drug companies provide treatment use); see also U.S. Food & Drug Administration, Center for Drug Evaluation and Research, Oncology Tools, Access to Unapproved Drugs, http://www.fda.gov/cder/cancer/access.htm (last visited Mar. 19, 2009) ("Treating a patient as an exception [to the study protocol] is at the discretion of the investigator and sponsor... ").
under the authorized IND; (ii) charging does not constitute commercial marketing of a new drug for which a marketing application has not been approved; (iii) the drug is not being commercially promoted or advertised; and (iv) the sponsor of the drug is actively pursuing marketing approval with due diligence.\textsuperscript{113}

The sponsor must inform the FDA, in writing, of its plan to charge patients prior to beginning its charging practice.\textsuperscript{114} Sponsors may only charge an amount "necessary to recover costs of manufacture, research, development, and handling of the investigational drug."\textsuperscript{115}

\textbf{2. Emergency Use}

The emergency use provision allows a sponsor to ship an investigational drug for a specified use when submission of a formal IND under 21 C.F.R. § 312.23 (general IND) or § 312.34 (treatment use) is not possible due to an emergency situation.\textsuperscript{116} The sponsor must request emergency use authorization via "telephone or other rapid communication means."\textsuperscript{117} Authorization almost always "will be conditioned on the sponsor making an appropriate IND submission as soon as practicable after receiving the authorization."\textsuperscript{118} Although the regulation does not give specific examples of what types of situations rise to the level of "emergency,"\textsuperscript{119} elsewhere the FDA states that this regulation "implicitly acknowledged" informal types of expanded access, such as compassionate use for a single patient, that the FDA has historically granted.\textsuperscript{120} Unlike the treatment IND program, the emergency use program does not specify criteria that a patient, investigational drug, or situation must meet in order to qualify for emergency use.\textsuperscript{121} The FDA does not make information about how often the emergency use program is used readily available to the public.

\begin{itemize}
\item \textsuperscript{113} 21 C.F.R. § 312.7(d)(2).
\item \textsuperscript{114} Id.
\item \textsuperscript{115} Id. § 312.7(d)(3).
\item \textsuperscript{116} Id. § 312.36. \textit{See also} 21 U.S.C. § 360bbb(a) (2007) (authorizing the FDA to allow access to investigational drugs in emergency situations).
\item \textsuperscript{117} 21 C.F.R. § 312.36.
\item \textsuperscript{118} Id.
\item \textsuperscript{119} \textit{See id.} Although the FDA has issued guidance regarding large-scale emergency situations, such as public health or military crises, that guidance is not relevant to a discussion of individual patients' access. \textit{See U.S. Food and Drug Administration, Guidance: Emergency Use Authorization of Medical Products, http://www.fda.gov/oc/guidance/emergencyuse.html} (last visited Nov. 8, 2008).
\item \textsuperscript{120} Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. 75,147, 75,148-49 (proposed Dec 14, 2006) (to be codified at 21 C.F.R. § 312).
\item \textsuperscript{121} \textit{Compare} 21 C.F.R. § 312.34 (outlining the criteria for an investigational drug to be used for treatment use), and § 312.35 (listing protocol for treatment use), \textit{with} 21 C.F.R. § 312.36 (failing to list any criteria for emergency use).
\end{itemize}
3. Individual Use

The Food and Drug Modernization Act of 1997 created an access option for individual patients. The statutory provision allows any person, acting through a licensed physician, to request from a sponsor or manufacturer individual access to an investigational drug for treatment of a serious disease. Four conditions must be met before individual access is granted. First, the physician must determine that no alternative to the investigational drug exists for the patient and that the probable risk to the patient from using the investigational drug is not greater than the risk due to the serious disease. Second, “sufficient evidence of safety and effectiveness to support the use of the investigational drug” must exist. Third, individual use of the investigational drug must not interfere with the clinical investigation of the drug. Finally, the sponsor must submit a protocol describing the use of the investigational drug in a single patient or a small group of patients. Unlike the treatment and emergency use programs, the personal use program is not explained in a formal FDA regulation. Similar to the emergency use program, it is not clear how often the individual use option is used.

4. Disease-Specific Access Programs

There are two disease-specific expanded access programs, one for HIV/AIDS patients and one for cancer patients, that are similar to the treatment IND program. In response to the HIV/AIDS epidemic, the Public Health Service developed the parallel track system for persons living with HIV/AIDS. The parallel track system is “designed to expand the availability of promising investigational agents and to make these agents more widely available to people with AIDS and other HIV-related diseases who have no therapeutic alternatives and who cannot participate in the controlled clinical trials.” To achieve this purpose, parallel track studies enroll patients

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124. Id.
125. Id. § 360bbb(b)(1).
126. Id. § 360bbb(b)(2).
127. Id. § 360bbb(b)(3).
128. Id. § 360bbb(b)(4).
131. Expanded Availability of Investigational New Drugs Through a Parallel Track
ineligible for clinical trials, for example because they are too sick to meet the inclusion criteria.\textsuperscript{132} The parallel studies do not have a control group and run concurrently with traditional clinical trials.\textsuperscript{133} Sponsors must develop and submit a protocol for parallel access in order for their investigational drug to be studied in this system.\textsuperscript{134} The FDA approves or denies the protocol after consulting with the National Institutes of Health AIDS Research Advisory Committee.\textsuperscript{135} As of 2005, the clinical investigation of only one drug, stavudine, had been conducted using the parallel track system.\textsuperscript{136}

To provide expanded access to cancer patients, the “Group C” treatment IND program was developed jointly by the FDA and the National Cancer Institution (NCI).\textsuperscript{137} Similar to the treatment IND program, this program is intended to provide access to large groups of patients. Investigational drugs used for Group C are usually undergoing or have completed Phase 3 clinical trials and must have demonstrated “evidence of relative and reproducible efficacy in a specific tumor type.”\textsuperscript{138} The drugs are distributed by the National Institutes of Health, under NCI protocols, to physicians who administer the drugs to patients for treatment purposes.\textsuperscript{139}

\textbf{C. How Do U.S. Expanded Access Options Compare to Programs in Canada and Europe?}

Other developed nations address expanded access in a variety of ways, while some do not address the issue at all. For example, Canada’s “Special Access Programme” closely parallels the U.S. individual use or emergency use programs.\textsuperscript{140} Canada allows seriously ill patients to access pre-market drugs on a case-by-case basis.\textsuperscript{141} A patient’s physician must request the drug for the patient. The physician is responsible for ensuring that there is credible evidence to support the use of the drug and that the patient is informed of the

\begin{flushright}
132. \textit{Id.} at 13,257.
133. \textit{See id.} at 13,252-53.
134. \textit{See id.} at 13,252.
135. \textit{See id.}
136. \textit{Expanded Access}, supra note 99. Although only stavudine has undergone clinical investigation through the parallel track system, eleven other HIV/AIDS drugs have undergone clinical investigation with a treatment IND program. \textit{See id.}
139. \textit{Id.}
\end{flushright}
risks and benefits. Health Canada, the responsible department in the Canadian government, makes "every effort" to review special access applications within twenty-four hours, unlike the FDA, which does not specify how quickly it will review applications. Drug manufacturers "have the final word" regarding the approval of the application and are permitted to put restrictions on the special access use, including charging the patient for the drug. Health Canada, unlike the FDA, is currently reviewing its Special Access Programme to determine how well the program is functioning and planning to publicly report its findings.

European Union member states administer their own expanded programs, and some member states do not have any expanded programs. Although no unitary "European" expanded access program exists, the European Union does advise member states regarding "compassionate use" programs for large groups of patients. For those member nations with compassionate use programs, the European Union recommends that patients receiving experimental drugs have a serious or life-threatening illness with no other treatment options and that the drugs should be undergoing clinical investigation. Unlike the United States, the European Union recommends that member states do not allow patients to receive experimental drugs for off-label use.

The European Union also has programs for "orphan" drugs, which are intended to treat rare illnesses or are drugs for which manufacturers otherwise need incentives to produce because of economic reasons.

D. How Well Do the Current U.S. Expanded Access Options Work?

Since the inception of formal expanded access programs in the United States, a large number of patients have gained access to investigational drugs outside of clinical trials. According to FDA reports, around one hundred

142. *Id.*
143. *Id.*
144. *Id.*
147. For example, the U.K. has a program that allows patients to receive orphan drugs, but does not have a general emergency or compassionate use program. *See* INTERNATIONAL PHARMACEUTICAL LAW & PRACTICE § 18.04 (2007).
149. *Id.*
150. *Id.*
thousand patients have gained access to investigational drugs through its expanded access programs. Over 75,000 patients with HIV/AIDS have received access to drugs through expanded access programs, suggesting that only approximately 25,000 patients with a condition other than HIV/AIDS have received investigational drugs through expanded access programs.

Patients may perceive the number of current opportunities available for expanded access to be limited because the existing options may not be effectively communicated to patients. A search for "expanded access" on the NIH clinical trials registry, ClinicalTrials.gov, indicates that as of February 1, 2009, there are 101 expanded access protocols, of which 47 are seeking more volunteers, out of approximately 27,000 total clinical trials seeking more volunteers. Even if only a small fraction of the approximately 27,000 listed open clinical trials are eligible for expanded access programs, expanded access opportunities for patients are more limited than the opportunities to participate in clinical trials. The low number of expanded access trials resulting from the search may be due in part to ineffective search tools on the website. For example, if one uses the "advanced search" function on ClinicalTrials.gov and selects "expanded access studies" as the study type, a search yields only 67 total trials. Similarly, a California pancreatic cancer organization used data-mining techniques to find 435 trials accepting pancreatic cancer patients on ClinicalTrials.gov, whereas a search for "pancreatic cancer" on the website yielded only 98 trials.

It is not clear precisely how many applications for the expanded access mechanisms the FDA denies for failing regulatory requirements or because a sponsor declines to make its investigational drug available for expanded access. The current head of the Office of Oncology Drug Products stated that, in his first year and a half, the FDA had denied only one application for expanded access and had done so only because the child patient's parents had refused to give the child the standard treatment. However, if many patients,


154. See U.S. National Institutes of Health, ClinicalTrials.gov, http://www.clinicaltrials.gov/ (last visited Feb. 1, 2009) [hereinafter ClinicalTrials.gov]. ClinicalTrials.gov indicates that it has a total of 67,791 trials listed; by selecting the advanced search function, and limiting the search to trials with open recruitment, a list of approximately 27,000 trials is produced. See id.


156. See ClinicalTrials.gov, supra note 152.


like Abigail Burroughs, are requesting access to investigational drugs that are just beginning Phase 2 clinical trials, the FDA is likely turning down more applications for expanded access than this FDA official’s experience might suggest.\(^{159}\)

Similarly, it is difficult to determine precisely how many of the investigational drugs to which patients do gain treatment access are later found to be safe and effective. Only 33% of the investigational drugs that Abigail Alliance is seeking to access – the drugs that complete Phase 1 and are beginning Phase 2 clinical trials – are eventually approved.\(^{160}\) Moreover, a majority of drugs that fail to reach the market do so because of problems with safety or effectiveness. Of all of the drugs that drop out of the approval process, 37.6% are withdrawn due to insufficient effectiveness, 19.6% are withdrawn due to safety concerns, 33.8% are withdrawn due to economic considerations, such as a commercial market that is too small, and 9.0% are withdrawn due to other problems.\(^{161}\) Conversely, patients and access advocacy groups may argue that patients, especially those notified of a particular investigational drug by their doctor, are seeking access to especially promising drugs that are more likely to be among those destined for approval.\(^{162}\)

Without more comprehensive data, it is unknown how many patients currently are being treated with investigational drugs through expanded access, how many patients want to be treated with investigational drugs but are denied access by the FDA, how often sponsors refuse to participate in expanded access options, and whether patients who do gain access are being treated with drugs that are eventually found to be safe and effective. The FDA does not make this data readily available to the general public, and patient advocacy groups, like Abigail Alliance, have not yet pushed the FDA to publish such data.\(^{163}\)

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159. See 21 C.F.R. 312.34 (2008) ("[A] drug may be made available for treatment use under this section earlier than Phase 3, but ordinarily not earlier than Phase 2."). The media has covered a few stories of patients other than Abigail Burroughs who have been denied treatment access to investigational drugs. See, e.g., Kianna's Law, WALL ST. J., Nov. 15, 2005, at A22 (reporting on the story of Kianna Karnes, a woman who died of kidney cancer and was unable to gain expanded access to two investigational drugs).

160. DiMasi, Risks, supra note 34, at 303 fig.7. See also Kola & Landis, supra note 34, at 712 (finding only 5% of investigational cancer drugs are eventually approved).

161. DiMasi, Risks, supra note 34, at 304 fig.9.

162. Frank Burroughs has made a similar argument, claiming that Abigail Alliance has never “pushed” for a drug that was “rejected by the FDA.” Talk of the Nation: FDA Drug Approval Comes Too Late for Many Patients (National Public Radio broadcast Jul. 30, 2007). However, it is not clear that Abigail Alliance has only sought access to drugs that are eventually approved. In the same interview, Mr. Burroughs also says that Abigail Alliance worked with patients seeking Provenge and was disappointed when the FDA did not approve Provenge. Id. See also FDAnews, Judge Dismisses Parts of Provenge Lawsuit Against FDA, Dec. 3, 2007, http://fdanews.com/newsletter/article?issuelld=11066&articleId=101686 (last visited Jan. 2, 2009) (noting that the FDA is currently being sued for its failure to approve Provenge).
data.  

III. NO FUNDAMENTAL RIGHT TO ACCESS INVESTIGATIONAL DRUGS:  ABIGAIL ALLIANCE V. VON ESCHENBACH

Against this background of existing expanded access options and some uncertainty about their efficacy, Abigail Alliance first filed a Citizen Petition with the FDA and then filed a lawsuit against the FDA, in an attempt to further increase terminally ill patients’ access to investigational drugs.

A. Citizen Petition

In 2003, Abigail Alliance submitted proposed new regulations to the FDA, called “Tier 1 Initial Approval,” that would create a system of different levels of approval. A drug that completed Phase 1 trials and was determined to be safe enough for further study in humans, could receive “Tier 1 Initial Approval,” contingent on the sponsor diligently pursuing full approval. The sponsor would be permitted to market drugs approved at the Tier 1 level and to sell those drugs for a profit. The Tier 1 proposal did not explicitly address access for patients suffering from an illness that is not the drug’s indication, the situation that Abigail Burroughs faced. The FDA declined to accept Abigail Alliance’s proposal because it “would upset the appropriate balance that [the FDA is] seeking to maintain, by giving almost total weight to the goal of early availability and giving little recognition to the importance of marketing drugs with reasonable knowledge for patients and physicians of their likely clinical benefit and their toxicity.” Abigail Alliance next filed a Citizen Petition, a way to formally ask the administrative agency to take action, requesting that the proposed regulations be promulgated. The FDA did not respond to the Citizen Petition.

B. Abigail Alliance v. von Eschenbach

Following its unsuccessful attempt to change FDA policy through
administrative means, Abigail Alliance filed a complaint seeking to enjoin the FDA from preventing the sale of investigational drugs to terminally ill patients, on the grounds that the FDA's restrictive policy violates terminally ill persons' fundamental rights to privacy, liberty, and life. Specifically, Abigail Alliance sought access for mentally competent, terminally ill patients to investigational drugs that, during Phase I clinical trials, were shown to be sufficiently safe for further study in humans. The complaint further alleged that the FDA's existing expanded access programs were inadequate because sponsors were only able to charge patients the cost of the drugs and could not profit from the sale of unapproved drugs. According to Abigail Alliance, this system does not provide sufficient motivation for sponsors to participate in expanded access programs.

In *Washington v. Glucksberg*, the Supreme Court articulated the analysis courts use to determine whether a particular interest, like the one asserted by Abigail Alliance, is a protected liberty interest.

First, we have regularly observed that the Due Process Clause specially protects those fundamental rights and liberties, which are, objectively, deeply rooted in this Nation's history and tradition, and implicit in the concept of ordered liberty, such that neither liberty nor justice would exist if they were sacrificed. Second, we have required in substantive-due-process cases a careful description of the asserted fundamental liberty interest. If a protected liberty interest exists under this test, a court must determine whether the government action affecting that interest "is narrowly tailored to serve a compelling government interest." If no protected liberty interest exists, the government action affecting the interest must only be "rationally related to legitimate government interests."

Applying this test, the District Court dismissed Abigail Alliance's case for failure to state a claim, finding that terminally ill patients' access to investigational drugs was not a protected liberty interest, and the FDA policy of restricting access to investigational new drugs was rationally related to


170. Id.


172. 521 U.S. 702 (1997). In this case, respondents sought a declaration that Washington's ban on physician-assisted suicide was unconstitutional, because it violated terminally ill patients' substantive due process liberty interests to make the choice to die via physician-assisted suicide. The Supreme Court upheld the ban as constitutional, finding no protected liberty interest in physician-assisted suicide. *Id* at 782. The Supreme Court has also articulated a slightly different test to determine whether a protected liberty interest existed, grounded in "personal dignity and autonomy." *Abigail Alliance*, 445 F.3d at 476. However, since each of the decisions in the *Abigail Alliance* litigation applied a Glucksberg analysis, this paper only discusses that analysis in depth. See *Abigail Alliance*, 495 F.3d at 697; *Abigail Alliance*, 445 F.3d at 471; *Abigail Alliance*, 2004 U.S. Dist. LEXIS 29594, at *26-27.

173. Glucksberg, 521 U.S. at 720-21 (citations and internal quotations omitted).

174. *Id* at 721.

175. *Id* at 728.
legitimate state interests, such as protecting vulnerable patients from fraudulent cures.\textsuperscript{176} A three-judge panel of the D.C. Circuit heard the appeal of the District Court's decision. Relying on Glucksberg, the two-judge majority found that the District Court erred in dismissing the case.\textsuperscript{177} Judges Rogers and Ginsburg held Abigail Alliance had asserted a protected liberty interest, stating "... 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."\textsuperscript{178} The majority distinguished this case from Rutherford because laetrile had not been demonstrated to be safe in any clinical trials at any level, whereas Abigail Alliance sought access to drugs that had been determined to be safe enough for further study in humans.\textsuperscript{179} Judge Griffith dissented, arguing that no constitutionally protected interest in access to unapproved drugs exists and that balancing the uncertain risks and benefits of science is "for good reason, the historical province of the democratic branches."\textsuperscript{180} The D.C. Circuit remanded the case to the District Court to determine whether the FDA's policy barring access to post-Phase I investigational drugs was narrowly tailored to serve a compelling government interest.\textsuperscript{181}

On rehearing, the D.C. Circuit en banc vacated the panel's decision on an eight to two vote, again applying the Glucksberg analysis.\textsuperscript{182} First, the court assumed that mentally competent, terminally ill patients' right to access post-Phase I drugs, as described by Abigail Alliance, would satisfy the "careful description" prong of the Glucksberg analysis.\textsuperscript{183} The court next turned to the question of whether the asserted right was "deeply rooted in this Nation's history, legal traditions, and practices."\textsuperscript{184} The court rejected Abigail Alliance's first argument - that the asserted right was deeply rooted in our history - because the government historically did not interfere with the right of

\textsuperscript{176} See Abigail Alliance, 2004 U.S. Dist. LEXIS 29594, at *25-36.

\textsuperscript{177} Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach, 445 F.3d 470, 486 (D.C. Cir. 2006), vacated en banc, 495 F.3d 695 (D.C. Cir. 2007).

\textsuperscript{178} Id.

\textsuperscript{179} Id.

\textsuperscript{180} Id. at 487 (Griffith, J., dissenting).

\textsuperscript{181} Id. at 486


\textsuperscript{183} Id. at 702 (quoting Washington v. Glucksberg, 521 U.S. 702, 721 (1997)). Although the D.C. Circuit assumed that the asserted right met the careful description requirement so that it could reach the history and tradition argument, the court expressed doubt that the right as described by Abigail Alliance could ever be constitutionally required. See id. at 703 n.6. Abigail Alliance asserted a right to access drugs only after an administrative determination that a drug is safe for Phase 2 testing; the court found "it difficult to imagine how a right inextricably entangled with the details of shifting administrative regulations could be 'deeply rooted in this Nations' history and tradition and implicit in the concept of ordered liberty.'" Id. at 703 (quoting Glucksberg, 521 U.S. at 721).

\textsuperscript{184} Id at 703.
physicians to determine which drugs would be effective for their patients until the Kefauver-Harris amendments to the FDCA in 1962.\textsuperscript{185} The court cited the longstanding tradition of regulating drugs for safety, rather than effectiveness, as evidence that the FDA’s regulation of post-Phase 1 drugs was consistent with U.S. history.\textsuperscript{186} Additionally, the court noted that some regulation prior to the 1962 amendments did in fact monitor drug effectiveness.\textsuperscript{187} Finally, the court concluded that even if effectiveness of drugs was not significantly regulated prior to 1962, it would not be persuasive evidence of a deeply rooted right to unfettered access because the technology and the nature of the pharmaceutical industry have evolved significantly over history creating a need for new regulatory schemes.\textsuperscript{188}

The court also rejected Abigail Alliance’s argument that this right to “self preservation” was deeply rooted in common law doctrines of necessity,\textsuperscript{189} intentional interference with rescue, and the right to self-defense.\textsuperscript{190} The court dismissed the necessity doctrine argument because “Congress may limit or even eliminate a necessity defense that might otherwise be available. That is precisely what the FDCA has done.”\textsuperscript{191} The court held that the interference with rescue doctrine did not apply. In order to interfere with rescue, a person must “intentionally [prevent] a third person from giving to another aid necessary to his bodily security.”\textsuperscript{192} The aid that Abigail Alliance claimed the FDA had prevented – access to post-Phase 1 investigational drugs – was, by definition, not necessary because the drugs had not been shown to be safe or effective.\textsuperscript{193} Finally, the court rejected the right to self-defense as a ground for a protected liberty interest “[b]ecause terminally ill patients cannot fairly be characterized as using reasonable force to defend themselves when they take unproven and possibly unsafe drugs . . . .”\textsuperscript{194}

After finding that Abigail Alliance had not asserted a protected liberty interest, the court upheld the District Court’s conclusion that the FDA regulations were rationally related to a legitimate government interest.\textsuperscript{195} The majority concluded by noting that although the Constitution does not require that terminally ill patients be given treatment access to post-Phase 1 drugs, Abigail Alliance can seek to gain such access through democratic means, such as lobbying Congress.\textsuperscript{196}

\textsuperscript{185} Id.
\textsuperscript{186} See id. at 703-06.
\textsuperscript{187} Id. at 706.
\textsuperscript{188} Id. at 706-07.
\textsuperscript{189} The necessity doctrine covers “the situation where physical forces beyond the actor’s control rendered illegal conduct the lesser of two evils.” Id. at 707. The court noted that Abigail Alliance does not explain in detail how this doctrine applies to its case. Id.
\textsuperscript{190} Id. at 707.
\textsuperscript{191} Id. at 708.
\textsuperscript{192} Id. at 708 (emphasis added).
\textsuperscript{193} Id. at 709 n.15.
\textsuperscript{194} Id. at 710.
\textsuperscript{195} Id. at 712.
\textsuperscript{196} Id. Judge Griffith, who dissented in the panel decision, wrote the \textit{en banc} majority
The Supreme Court denied Abigail Alliance’s petition for certiorari on January 14, 2008.\(^{197}\) Several reasons may exist for the Supreme Court’s decision. Although the Court has not addressed the precise issue presented by Abigail Alliance, it has rejected several similar constitutional challenges to the FDCA.\(^{198}\) None of the circuit courts that have faced an issue similar to that presented in Abigail Alliance, with the exception of the D.C. Circuit panel, have found an affirmative right to access.\(^{199}\) Additionally, a nuanced, technologically complex question, such as determining how much information is enough to evaluate the safety of new drugs, may be better resolved by an administrative agency that has the necessary expertise or by Congress that possesses the institutional competence to balance different policy considerations.\(^{200}\) Even if the Court had granted certiorari and reversed the D.C. Circuit’s decision, Abigail Alliance was not assured victory; in order to accomplish its goal of access to post-Phase 1 investigational drugs, the organization would have been required to demonstrate that the FDA regulations, including the provisions for expanded access, were not narrowly tailored to serve a compelling government interest.\(^{201}\)

The en banc D.C. Circuit’s decision only holds that there is no constitutional right to expanded access. It does not hold that there is any constitutional prohibition on such access, allowing room for expanding treatment access to investigational drugs through policy channels, by either regulatory or statutory changes.

**IV. POLICY LEVEL PROPOSALS TO CHANGE THE EXPANDED ACCESS OPTIONS**

Following the onset of litigation, Abigail Alliance and the FDA each put forth a proposal for change at the policy level that may achieve the Alliance’s goal of creating easier and broader access to investigational drugs.

**A. ACCESS Act**

With the support of Abigail Alliance, Senators Sam Brownback and James Inhofe proposed the Access, Compassion, Care, and Ethics for Seriously Ill Patients Act (ACCESS Act) in 2008.\(^{202}\) The Proposed ACCESS Act would

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\(^{197}\) Id., cert. denied, 128 S. Ct. 1069 (2008).

\(^{198}\) Id. at 710; United States v. Rutherford, 442 U.S. 544, 552 (1979). *See also* Gonzales v. Raich, 545 U.S. 1, 28 (2005) (interpreting *Rutherford* as indicating that “the dispensing of new drugs, even when doctors approve their use, must await federal approval”).

\(^{199}\) *Abigail Alliance*, 495 F.3d at 710 n.18.


\(^{201}\) *See* Dresser, *supra* note 198, at 10.

\(^{202}\) The ACCESS Act was first proposed in 2005. Press Release, United States Senator Sam Brownback, *Brownback Introduces ACCESS Act* (Nov. 3, 2005),
amend the “fast track products” section of the FDCA to create a tiered system of approval similar to the system proposed by Abigail Alliance’s Citizen Petition, and would alter other FDA practices, such as the use of statistical evidence to evaluate whether a particular drug is safe and effective.\textsuperscript{203}

1. Tiered Approval System

For “Compassionate Investigational” approval under the ACCESS Act, a drug must show “preliminary evidence that the product may be effective against a serious or life-threatening condition or disease” following Phase 1 trials,\textsuperscript{204} and the sponsor must assure the FDA that it will continue clinical investigation to try to obtain “Final Approval.”\textsuperscript{205} Compassionate Investigational approval is “based upon multiple considerations that shall include clinical evaluation and unmet patient needs.”\textsuperscript{206} The labels on Compassionate Investigational drugs would inform consumers that they are for patients who have exhausted all treatment options with Final Approval and “unsuccessfully sought treatment, or obtained treatment that was not effective, with an investigational drug, biological product, or device for which such individual is a reasonable candidate.”\textsuperscript{207} It is not clear whether patients diagnosed with an illness other than the desired drug’s indication would be eligible for access to Compassionate Investigational drugs under this scheme. It is possible such patients would be eligible for access, similar to the way patients currently can be prescribed any FDA-approved drug through the practice of “off-label use.”\textsuperscript{208} Finally, all patients receiving Compassionate Investigational drugs would be required to give written informed consent, including consent for the sponsor or manufacturer to collect data about the patient, and waive the right to sue the sponsor or manufacturer.\textsuperscript{209}

“Accelerated Approval” presumably follows Phase 2 clinical studies, although the ACCESS Act does not make that explicit. Approval at the

\textsuperscript{203} See ACCESS Act, S.3046, 110th Cong. (2008).
\textsuperscript{204} Id. at § 3.
\textsuperscript{205} Id.
\textsuperscript{206} Id.
\textsuperscript{207} Id. The language describing the second prong of the labeling requirement is not entirely clear, but seems to imply that the patient must first seek access to the investigational drug through clinical trials or expanded access programs, before purchasing the drug as a Compassionate Investigational product.
\textsuperscript{208} U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INSTITUTIONAL REVIEW BOARDS, supra note 136.
\textsuperscript{209} S.3046 § 3. This waiver may not be an enforceable contract. Generally, a manufacturer of a defective or dangerous product is subject to tort liability, even if the purchaser signed a contract waiving the right to sue. See RESTATEMENT (SECOND) CONTRACTS § 195(3). A manufacturer may be more likely to be exempt from liability for the fairly negotiated sale of an experimental product. See id.
accelerated level requires only that the sponsor commit to pursuing Final Approval, and there are "data and information that the drug... has an effect on a clinical endpoint, or a surrogate endpoint, or biomarker that is reasonably likely to predict clinical benefit to a patient."\textsuperscript{210} Accelerated Approval does not include consent and waiver requirements like those required for Compassionate Investigational Access.\textsuperscript{211} Both Compassionate Investigational and Accelerated products may be subject to expedited withdrawal if the sponsor fails to conduct continuing clinical investigation, further investigation does not demonstrate a clinical benefit of the drug, any other evidence suggests the product is not safe or effective for the target population, or the sponsor distributes false or misleading promotional materials about the product.\textsuperscript{212}

Final Approval constitutes full approval of the product, as exists under the current FDCA provisions.\textsuperscript{213}

2. Other Changes

The ACCESS Act also contains several changes to the FDCA that are separate from the tiered approval system. To replace the current fast track system, the ACCESS Act would create an Advisory Committee to facilitate accelerated full approval of drugs intended to treat serious or life-threatening illnesses.\textsuperscript{214} The Committee would be comprised of eleven members, two of whom must be "representatives of patient interests."\textsuperscript{215} The Secretary of the Department of Health and Human Services would be permitted to delegate decision-making authority for a particular drug to the Committee.\textsuperscript{216}

The ACCESS Act would require that the FDA "establish a new program to expand access to investigational treatments for individuals with serious or life threatening conditions and diseases."\textsuperscript{217} The FDA would be required to promulgate written guidance that describes the new programs, encourages submission of Compassionate Investigational and Accelerated applications, and facilitates access to investigational drugs without undue delay.\textsuperscript{218} The ACCESS Act aims to hasten the approval of investigational drugs by requiring the FDA to develop surrogate endpoints and biomarkers for use in clinical investigation, and to place equal weight on "clinical judgment and statistical analysis in evaluation of the safety and effectiveness of drugs."\textsuperscript{219}

The ACCESS Act would mandate the publication of all investigational drugs currently under study.\textsuperscript{220} This requirement does not represent a

\textsuperscript{210} S.3046 § 3.
\textsuperscript{211} See id.
\textsuperscript{212} See id.
\textsuperscript{213} See id. § 3(d).
\textsuperscript{214} Id. § 3(g).
\textsuperscript{215} Id.
\textsuperscript{216} Id. § 3(h).
\textsuperscript{217} See id. § 4.
\textsuperscript{218} See id.
\textsuperscript{219} See id.
\textsuperscript{220} See id.
significant change to FDA practice. ClinicalTrials.gov already serves as a publicly accessible registry of all clinical trials, and clinical trials of investigational drugs targeted to serious illnesses are required to be published under current law.

Finally, the ACCESS Act does not explicitly address whether pharmaceutical companies could profit from the sale of Compassionate Investigational drugs or investigational drugs in expanded access programs. Perhaps, because Compassionate Investigational drugs would be "approved," pharmaceutical companies would be allowed to charge patients more than cost. Additionally, the ACCESS Act would establish a five-year period during which Medicare would cover Compassionate Investigational drugs, collect information regarding the utilization rates of the drugs, and make recommendations to Congress at the end of the five-year period regarding continued coverage.

B. FDA Proposed Rule: Expanded Access to Investigational Drugs for Treatment Use

After the now-vacated D.C. Circuit panel's opinion in Abigail Alliance, the FDA issued a Proposed Rule that would modify its existing expanded access programs. Although the Rule was not a major departure from the status quo and has not yet been adopted, it does propose constructive changes that would clarify the expanded access programs. The Proposed Rule would amend the Code of Federal Regulations to create three types of expanded access programs that differ based on the number of patients they are intended to serve. The rule proposes three programs: one program for individual patients, which would also cover emergency access; one for "intermediate-size patient populations;" and one for larger patient populations that would be analogous to the current treatment IND program. In order to be eligible for any of the programs, the patient must meet four criteria: (1) the patient must have a serious or life-threatening disease; (2) there must be no satisfactory treatment available other than the investigational drug; (3) the potential benefit to the patient of using the investigational drug must outweigh the potential health risks of using the drug; and (4) providing the expanded access must not interfere with the clinical investigation. The primary differences between the proposed rule and the existing regulations are that the proposed rule clarifies the different expanded access options and the costs that sponsors are permitted to pass onto patients, and it creates an access option that would

221. ClinicalTrials.gov, supra note 152.
222. See Wadman, supra note 153, at 175.
223. See S.3046 § 5.
225. See id.
226. Id. at 75,150-51.
227. See id. at 75,150-52, 75,166-67.
explicitly allow off-label expanded access.

1. Access for Individual Patients

For an individual patient to obtain an investigational drug for treatment use outside of a clinical trial, the patient's physician must determine that the benefit of using the investigational drug outweighs the risk for that particular patient, and the patient must not be able to access the drug through a clinical trial or other type of expanded access program. The Proposed Rule creates several safeguards; it limits the treatment to "a single course of therapy for a specified duration," and requires physicians to provide a written summary of the patient's use, including a discussion of any unexpected adverse events, when the treatment concludes. If a "significant number" of individual patients submit applications for the same investigational drug, the FDA may ask the sponsor to submit an application for an intermediate-size or treatment access program. This section also permits emergency use in a manner very similar to the current emergency use regulation. This proposed regulation clarifies when and how individual patients may receive investigational drugs.

2. Intermediate-Size Patient Populations

The intermediate-size patient population program is the most innovative part of the proposed rule. This program would allow expanded access to drugs in three situations. First, patients may be allowed access if a drug is not being developed through a full clinical investigation because the sponsor cannot enroll enough participants in clinical trials due to rarity of a disease. Second, patients who do not meet clinical trial enrollment criteria, for example, because they have a disease or a stage of the disease other than the one being studied, or are too sick, may gain access to drugs that are being developed fully through all stages of clinical investigation. This prong is the only proposal for change that would explicitly address off-label use of experimental drugs, the situation that Abigail Burroughs faced. Third, patients may gain access to drugs that have been taken off the market due to safety concerns or a failure to meet post-approval requirements. Additionally, patients may access drugs with the same active ingredient as a drug that has been taken off the market or

228. Id. at 75,153, 75,167
229. Id. at 75,167.
230. Id.
231. Compare id. (allowing requests for expanded access via phone, facsimile, or other means of electronic communication, "[i]f there is an emergency that requires the patient to be treated before a written submission can be made"), with 21 C.F.R. § 312.36 (2007) (allowing requests for expanded access "by telephone or other rapid communication means," when an emergency "does not allow time for submission of an IND").
233. See id.
234. See id.
is no longer on the market due to a shortage.\textsuperscript{235}

In addition to meeting one of these three criteria, data must suggest the drug is safe enough to justify a clinical trial with the number of patients expected to take the drug through expanded access, and there must be preliminary evidence of its effectiveness.\textsuperscript{236} The application must include this data and inform the FDA whether the drug is being actively developed (or, if it is not being developed, why not) and why the patients cannot access the drug through traditional clinical trials.\textsuperscript{237} Finally, the proposed rule provides safeguards of both FDA and sponsor oversight.\textsuperscript{238}

3. Treatment IND or Treatment Protocol

For large groups of patients, the Proposed Rule creates an expanded access program that is almost identical to the existing treatment IND program.\textsuperscript{239} The differences between the two programs are not significant.

4. Permissible Charges

The FDA’s Proposed Rule does not permit pharmaceutical companies to profit from expanded access programs; it allows sponsors and manufacturers to recover only the direct costs of producing the drug and the costs associated with monitoring the expanded access protocol and meeting the expanded access requirements.\textsuperscript{240} The Proposed Rule maintains most of the previous charging regulations, expanding those charging policies to cover all three new expanded option programs.\textsuperscript{241} Additionally, it clarifies the definition of recoverable direct and indirect costs by providing examples of recoverable costs, such as the cost of raw materials to produce the drug.\textsuperscript{242}

\textsuperscript{235} 71 Fed. Reg. at 75,154, 75,167.
\textsuperscript{236} Id. at 75,167-68.
\textsuperscript{237} Id.
\textsuperscript{238} See id. at 75,168.
\textsuperscript{239} Compare id. at 75,168 (allowing treatment access when (1) patients have a serious or life-threatening condition, (2) the potential benefits of the drug justify the potential risks, (3) expanded access will not interfere with clinical trials, (4) the drug is under investigation in a clinical trial or clinical trials have been completed, and (5) the sponsor is pursuing full approval), with 21 C.F.R. § 312.34 (2007) (allowing treatment access when (1) patients have a serious or life-threatening condition, (2) the patient has no other satisfactory alternative, (3) the drug is under investigation in a clinical trial or clinical trials have been completed, and (4) the sponsor is pursuing full approval), and 21 U.S.C. § 360bbb(c)(5) (2008) (adding to the regulations that treatment access must not interfere with clinical trials).
\textsuperscript{241} See id. at 75,169-70.
\textsuperscript{242} See id. at 75,172-73.
V. POLICY IMPLICATIONS OF CHANGING THE EXPANDED ACCESS PROGRAMS

Proposed changes to the expanded access mechanisms raise a variety of policy concerns. In order to evaluate whether the FDA should change its expanded access options to one of the systems proposed by the ACCESS Act and the FDA or to a system not yet conceived, this Part examines the policy concerns raised by expanded access programs generally and those that would allow post-Phase I and off-label access to investigational drugs.

A. Comprehensive Data

Without clear and comprehensive data regarding how many patients are informed of expanded access programs through the current system, how many patients try and fail to gain access to investigational drugs and why they fail, and how safe and effective the investigational drugs sought for access ultimately are, it is difficult to determine what changes, beyond clarification of the regulations, should be made. 243 If the FDA collected data about the functioning of the system and made it publicly available, stakeholders—including pharmaceutical companies, physicians, patients, and patient advocacy groups—may be better able to assess the system. Such transparency might also encourage patients and patient advocacy groups to have greater trust in the FDA. 244 Of course, many patient advocacy groups might simply disagree with the FDA about whether patients have a right to post-Phase I and off-label access to investigational drugs. Information is not likely to bridge such wide gaps in opinion, but it will improve assessment of each side's arguments.

B. Safety and Expanded Access

One policy concern raised by expanded access programs is whether they strike the appropriate balance between ensuring the safety of approved drugs and increasing access to unapproved drugs. 245 Over the past few years, in addition to calls for reform of the FDA’s expanded access programs, the FDA has been criticized for not adequately ensuring the safety of the products that are approved. 246 In one high profile example of such criticism, the FDA approved the painkiller Vioxx without requiring additional clinical trials, despite knowing that Vioxx might pose significant cardiac risks. 247 Patients

243. Canada is currently collecting such data to evaluate its Special Access Programme. See SAP – Comprehensive Review, supra note 143.


245. See, e.g., Jacobson & Parmet, supra note 1, at 206-07.

246. See, e.g., FUTURE OF DRUG SAFETY, supra note 34; Sheila Weiss Smith, Sideline Safety – The FDA’s Inadequate Response to the IOM, 357 NEW ENG. J. MED. 960, 960 (2007); Marian Burros, F.D.A. Inspections Lax, Congress is Told, N.Y. TIMES, July 18, 2007, at C3.

247. See FUTURE OF DRUG SAFETY, supra note 34, at 65; Charles Steenburg, The Food and
taking Vioxx were later found to have five times as many heart attacks as the patients taking a traditional painkiller had. Safety concerns are cited as the reason for attrition in twenty to thirty percent of the drugs that drop out of the clinical investigation process. Approximately thirty to forty percent of failed investigational drugs drop out due to a lack of effectiveness. Risks of using investigational drugs include a lack of effectiveness, as well as safety risks such as hastening death or an increase in the pain and suffering experienced by the patient. The high attrition rate of post-Phase 1 drugs suggests that allowing access to such drugs poses a significant possibility of increased risks to patients. This risk of adverse effects also may be particularly high when patients obtain off-label access to investigational drugs because there would be little or no actual data about the drug’s effect on their condition or adverse events in their patient population. From an ethical perspective, such an increase in risk might not be justifiable because the benefits to the patients are unknown and may be unlikely.

C. Interference with the Approval Process

Expanded access programs have the potential to interfere with clinical trials by reducing the number of patients who enroll in traditional clinical trials and creating additional opportunity for adverse events to occur. If an investigational drug is available through expanded access, patients may be reluctant to enroll in clinical trials, where they risk receiving the control rather than the investigational drug, when they could gain certain access to the investigational drug outside of clinical trials. Physicians also might encourage feel pressure to help their patients seek expanded access instead of enrolling in clinical trials. In the early 1990s, many researchers felt that expanded access significantly decreased enrollment in the clinical trials of didanosine, a drug that treats HIV/AIDS. Sponsors’ concerns regarding
enrollment may be particularly strong if the FDA allowed expanded access at the post-Phase 1 stage, because such access might affect Phase 2 as well as Phase 3 trials.\textsuperscript{257} The current FDA treatment use program, as well as the programs proposed in the FDA’s Proposed Rule and the ACCESS Act, require patients to exhaust clinical trial options before gaining expanded access. If such requirements have been effective in preventing expanded access mechanisms from interfering with clinical trial enrollment, the FDA may want to publicize that success to assure sponsors that expanded access does not threaten enrollment in their clinical trials.

Pharmaceutical companies also have expressed reluctance to make an investigational drug available through expanded access because of their concern that an adverse event in the expanded access protocol would prevent their drug from receiving approval.\textsuperscript{258} The director of the Office of Oncology Drug Products stated that many companies are afraid “the FDA will find some toxicity in the expanded-access program . . . and the drug will be killed.”\textsuperscript{259} None of the proposed changes to the current expanded access mechanisms address this concern.\textsuperscript{260} Similar to enrollment concerns, fears regarding adverse events may be heightened by the prospect of post-Phase 1 and off-label expanded access because such access would enlarge the pool of patients who can access investigational drugs, creating more opportunities for adverse events to occur. The FDA cannot ignore evidence of toxicity discovered in expanded access protocols, but it is not clear whether adverse events in expanded access programs have prevented any products from receiving approval. By working with the pharmaceutical industry, the FDA may be able to develop modified access regulations that address this fear while still protecting patient safety. For example, the FDA may determine it is scientifically justified to weigh adverse events not involving severe toxicity that occur in patients with an illness other than the target condition differently than adverse events in the target population. However, these issues are particularly difficult because workable solutions may depend on whether the FDA would be scientifically justified in weighing adverse events differently when the drug is used in a non-target population.

Expanded access programs’ potential to interfere with the clinical trials process has implications beyond pharmaceutical companies’ willingness to participate in them. Interference with clinical trials could negatively impact public health by preventing potentially effective treatments from reaching the market.\textsuperscript{261} The Food and Drug Modernization Act of 1997 and the FDA’s Proposed Rule wisely include provisions allowing the FDA to reject expanded

\textsuperscript{257} Allowing patients off-label access to an investigational drug likely does not pose clinical trial enrollment problems because such patients do not have the condition that would allow them to enroll in the clinical trials.

\textsuperscript{258} See Bethan Hughes, Resolving the Access Dilemma, 6 Nature Rev. Drug Discovery 769, 770 (2007); Groopman, supra note 9, at 45.

\textsuperscript{259} Groopman, supra note 9, at 45.

\textsuperscript{260} See Hughes, supra note 256, at 770.

\textsuperscript{261} See Bender et al., supra note 252, at 4.
access applications if the access would interfere with the clinical investigation.262 These provisions balance the tension between the private desire to make choices about one's own health care and the public health benefit of knowing the risks and benefits of drugs on the market that is inherent to the drug regulation system.

D. Sponsors’ Costs

Pharmaceutical companies may be concerned about the cost of participating in expanded access programs, because they cannot profit from investigational drugs, and they incur administrative costs related to running the expanded access protocol. Such concerns may be heightened if the FDA increases the size of the expanded access patient pool through extending expanded access programs to include post-Phase 1 drugs and off-label access. The FDA’s Proposed Rule stipulates that pharmaceutical companies can charge patients for both the costs of producing the investigational drug for treatment use and the administrative costs of overseeing the treatment use program.263 The pharmaceutical industry has found this clarification of the FDA’s charging policies beneficial.264 The ACCESS Act goes further, allowing companies to market and sell their “Tier 1” drugs, without requiring that it be sold without profit.265

Both of these proposed changes to the system attempt to alleviate some of the financial burdens associated with sponsors’ participation in expanded access programs. However, even if the pharmaceutical companies were permitted to market investigational drugs under the ACCESS Act provisions, they would probably not be able to entirely offset their costs.266 Drug manufacturers probably could not charge full market price for post-Phase 1 drugs.267 The expanded access market is small because expanded access is only available to those terminally ill patients who have exhausted all approved treatments and are unable to enroll in clinical trials.268 Medicare, Medicaid, and private insurance companies do not pay for investigational drugs.269 Additionally, the costs of investing in production capability are high; pharmaceutical companies are not likely to invest in large-scale production with little certainty that post-Phase 1 drugs will ever receive full approval and

264. See Hughes, supra note 258, at 770.
265. See S. 1956.
266. See Okie, supra note 4, at 440.
267. See id.
269. Groopman, supra note 9, at 45.
the concomitant access to a large market.\textsuperscript{270}

Allowing pharmaceutical companies to profit from the expanded access programs may not only fail to relieve the financial burdens, it may also increase public distrust of the pharmaceutical companies. Public opinion of pharmaceutical companies is not positive.\textsuperscript{271} Many people already believe that pharmaceutical companies care more about their profits than about patients' health; allowing pharmaceutical companies to profit from the sale of investigational drugs, not proven to be safe or effective, to vulnerable, terminally ill patients may exacerbate the negative public image of the pharmaceutical industry.\textsuperscript{272} The FDA's pricing scheme seems to better balance the need to encourage pharmaceutical companies to participate in expanded access programs, while maintaining public trust in the approval process. The lack of certain financial incentives, as well as the potential for interference with the clinical trial system, suggests that pharmaceutical companies may not be eager to participate in and may not benefit from a post-Phase 1 market that the ACCESS Act would create.\textsuperscript{273} If expanded access programs become more widely available or required, pharmaceutical companies may have to adjust the pricing of drugs that are eventually approved to account for the costs of expanded access programs.

\textbf{E. Patients' Costs}

The current regulations, the FDA Proposed Rule, and the ACCESS Act only allow access to investigational drugs for those patients who can afford to purchase the drugs. Private health insurance, Medicare, and Medicaid have not paid for treatment access to investigational drugs in the past and probably will not pay for such access in the future.\textsuperscript{274} Even if patients are only being charged for the cost of the drugs, that cost could be unaffordable for many low-income persons.\textsuperscript{275} All expanded access programs, but particularly those programs that would increase the cost of the drugs by allowing pharmaceutical

\textsuperscript{270} Currie, supra note 130, at 321-23. For example, one of the drugs that Abigail Burroughs sought to access outside of clinical trials, gefitinib, was easier and cheaper to manufacture than the other drug, cetuximab. Even though both drugs were EGFR inhibitors intended for similar patient populations, only gefitinib was ever widely distributed through an expanded access program. See Editorial, \textit{A Delicate Balancing Act}, supra note 254, at 685.


\textsuperscript{273} See Currie, supra note 130, at 323.

\textsuperscript{274} See Groopman, supra note 9, at 45.

\textsuperscript{275} The cost of developing a new drug was estimated to be eight hundred and two million dollars in 2001. Dimasi et al, \textit{Price of Innovation}, supra note 30, at 167 fig.2. Even if the cost of producing drugs for and administering a treatment program is a very small fraction of the overall cost of developing a drug, drugs made available through treatment programs are not likely to be affordable for most low-income persons.
companies to sell the drugs for a profit, create the possibility that cutting-edge therapies will be available only to wealthy, terminally ill persons. Low-income persons would still have the opportunity to access investigational drugs through clinical trials, but they would face the risk of receiving the current treatment rather than the desired investigational drug. Given the low approval success rates of post-Phase 1 drugs, low-income persons would not necessarily have access to worse care than high-income persons; but a system that provides low-income persons with more limited choices than it provides to high-income persons raises concerns about further exacerbating inequality in health care options and implicating the FDA and the researchers in the unequal distribution of resources. There is no clear, feasible solution to this problem within our current tiered health care financing system.

**F. Communicating the Risks and Benefits of Investigational Drugs**

Expanded access programs pose a challenge to the scientific community regarding how best to communicate the limited knowledge about the risks and the benefits of investigational drugs. Programs that provide post-Phase 1 and off-label access to investigational drugs present the greatest challenges, because there is very limited knowledge about the risks and the benefits of such access to investigational drugs for a particular patient.

On an individual level, the informed consent process is the mechanism through which patients learn about the risks and the benefits. In a treatment use setting, when patients are using investigational drugs, not as study participants but for treatment, the risk of therapeutic misconception may be particularly high. Even when patients are told they are participating in a research study that is not intended to benefit them personally in any way, patients tend to exhibit a robust therapeutic misconception. In order to make every effort to ensure patients understand the uncertain nature of investigational drugs, physicians administering investigational drugs for treatment use should be careful to employ the most effective means of informing patients possible. Such methods may include providing the relevant information more than once, testing patient comprehension of the

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277. See Talbott, supra note 92, at 318.

278. Cf. Caplan, supra note 249, at 2 ("Nor is it clear that those who are terminally ill can make the requisite autonomous risk/benefit decision to use a new drug, device or vaccine.").

279. See id. at 2; Charles W. Lidz & Paul S. Appelbaum, The Therapeutic Misconception: Problems and Solutions, 40 MED. CARE (SEPT. SUPP.) V-55, V-57 (2002); see also Steven Joffe et al., Quality of Informed Consent in Cancer Clinical Trials: A Cross-Sectional Survey, 358 LANCET 1772, 1775 tbl.2 (2001) (finding almost half of participants in cancer clinical trials mistakenly thought the experimental treatment was the standard treatment for their type of cancer, and almost 30% believed that the experimental treatment was "proven" to be the best treatment for their type of cancer).

280. See Talbott, supra note 92, at 318.
pertinent information, and using a physician who is unaffiliated with the development of the drug to help explain the risks and benefits.\textsuperscript{281} Sponsors also should be required to disclose all known safety and effectiveness information to the physicians administering the investigational drug, even if such information is proprietary.\textsuperscript{282} None of the proposed changes to the expanded access programs explicitly require these extensive informed consent procedures.

Expanded access programs also raise large-scale questions about how science should be advertised and how the public should be informed of the risks and benefits of investigational drugs. Under the current expanded access programs, it is unclear exactly how most patients are informed of the opportunity to gain early treatment access to investigational drugs. Many patients likely learn about investigational drugs through their physicians, through patient advocacy groups like Abigail Alliance, or through clinical trial listings on registries, such as ClinicalTrials.gov. Under the ACCESS Act, pharmaceutical companies would be permitted to conduct limited marketing campaigns for post-Phase I drugs. The FDA would have to determine how best to regulate such marketing to ensure that it adequately informed consumers of the uncertainty regarding the safety and effectiveness of such drugs. Apart from marketing under the ACCESS Act, the FDA, pharmaceutical companies, or other stakeholders may want to consider how to best inform patients of expanded access opportunities and the uncertainty inherent to them.

**G. Physician and Sponsor Liability**

Allowing patients post-Phase I and off-label expanded access to investigational drugs may create increased risks of malpractice liability for the physicians who oversee a patient’s expanded access use and tort liability for drug manufacturers.\textsuperscript{283} Physicians may face traditional malpractice liability for recommending an expanded access protocol to a patient that does not prove successful.\textsuperscript{284} Under expanded access protocols, physicians also have oversight responsibilities in addition to their traditional duties as a physician, such as reporting adverse events to the sponsors, and may face liability for failing to perform these duties.\textsuperscript{285} Similarly, sponsors may face traditional tort liability if adverse events occur or if they decline to permit expanded access to


\textsuperscript{282} See Jacobson & Parmet, supra note 1, at 206.

\textsuperscript{283} See Talbott, supra note 92, at 317-18.

\textsuperscript{284} See id. at 317.

\textsuperscript{285} See id.
This possibility of increased liability may be a disincentive for physicians and sponsors to participate in expanded access programs, particularly for post-Phase 1 drugs, which are less likely to be safe and effective than more developed drugs.

The ACCESS Act attempts to safeguard physicians and drug manufacturers from this increased possibility of liability through a waiver. Unless enacted through legislation such as the ACCESS Act, such a waiver might be invalid as an unenforceable contract contrary to public policy.

Typically, two parties cannot contractually relieve one party of all tort liability for its actions. Furthermore, some have suggested the research community may not want to be involved with asking patients to relinquish their right to sue. However, a situation in which a competent adult has knowingly chosen to use an experimental product may be one situation in which a waiver of liability is not against public policy. If the FDA wishes to encourage sponsors and physicians to participate in expanded access programs, it will need to address their liability concerns.

VI. RECOMMENDATIONS

Of the existing formal proposals for change, the FDA’s Proposed Rule best balances the policy problems raised by expanded access programs. The Proposed Rule clarifies the expanded access programs, for example, by making explicit the currently implicit individual use program. It maintains the current balance between ensuring product safety and allowing terminally ill patients access to investigational drugs, which seems appropriate without data suggesting patients are routinely denied safe and effective investigational drugs. The Proposed Rule also strikes a balance between providing access and preventing disruption of the clinical trial process through its explicit provision prohibiting access that interferes with clinical trials. It explicitly addresses the needs of terminally ill patients who are excluded from clinical trials because, like Abigail Burroughs, their disease is not the exact condition being studied. The Rule does not grant the broad post-Phase 1 access that Abigail Alliance seeks, but such access may not be an appropriate balance of safety and risks. Finally, the Proposed Rule is supported by a variety of stakeholders, including pharmaceutical companies, professional medical organizations, and patient advocacy groups.

Beyond the Proposed Rule, the FDA should consider developing better

286. See id. at 318.
287. See ACCESS Act, S.1956 109th Cong. (2005); RESTATMENT (SECOND) CONTRACTS § 195(3) (1981). Explicit legislation may be the only means to override a public policy argument, assuming that the courts found that a waiver of liability in this circumstance is against public policy.
288. See RESTATMENT (SECOND) CONTRACTS § 195(3).
289. See Talbott, supra note 92, at 318.
290. See RESTATEMENT (SECOND) CONTRACTS § 195(3).
291. See Bristol, supra note 150, at 816. Abigail Alliance is not one of the patient advocacy groups that support the Proposed Rule. See id.
mechanisms for communicating about expanded access options with the public. First, similar to the Special Access Programme in Canada, the FDA could collect and disseminate to the relevant stakeholders information about how well the expanded access programs work in order to promote transparency and trust. Second, FDA may be able to encourage the National Institutes of Health and the Department of Health and Human Services to continue to improve the clinical trials registry to make it both more comprehensive and user-friendly, as well as consider other means for effectively communicating the availability of expanded access programs to patients. Third, the FDA could consider studying how best to communicate with the public at large about the risks and benefits of investigational drugs. Fourth, the FDA could expand its informed consent requirements. It could include an explicit requirement that the physicians conducting informed consent be given all available safety information about the investigational drug, even if that information is proprietary. The FDA also may want to encourage physicians and researchers to use an informed consent process that is more rigorous than the traditional process, particularly if the unapproved drug is at a relatively early stage in the clinical investigation process. A rigorous informed consent process may be a way both to alleviate sponsors’ and physicians’ concerns about liability, because it may provide some protection from liability and ensure that ethical obligations to adequately educate patients are met. Fifth, the FDA may want to consider ways in which it can gather and disseminate information to the drug sponsors regarding the functioning of the expanded access programs. For example, if the FDA has evidence that participation in expanded access programs does not significantly increase the risk that a drug will not be approved due to increased incidence of adverse events, communicating such information to sponsors may mitigate their concerns.

The FDA should also consider ways in which it can mitigate some of the other disadvantages of expanded access programs. The financial costs that sponsors face in such programs are a particularly intractable problem; the FDA cannot create a viable market for the sponsors without drastically altering the approval process, nor can the FDA reduce a sponsor’s production costs. The FDA may be able to mitigate some of the other disincentives perceived by sponsors and physicians, such as decreasing the risk of tort liability through requiring a rigorous informed consent process. Implementing many, if not all, of these recommendations may be contingent on the financial and personnel resources of the FDA.

VII. CONCLUSION

Although the courts have found no constitutional right to post-Phase 1 access of investigational drugs, expanded access programs can serve a valuable function of giving terminally ill patients the opportunity to determine their own

292. See SAP – Comprehensive Review, supra note 143.
293. See Talbott, supra note 92, at 318.
health care plan and maintain hope. Expanded access programs, in particular those that would grant post-Phase 1 access and off-label use access, also pose questions regarding how best to balance a myriad of policy and ethical concerns. The recommendations put forth in this Note aim to strike the appropriate balance between some of these concerns.