

**A STUDY IN FUTILITY:  
ABIGAIL ALLIANCE FOR BETTER ACCESS  
TO DEVELOPMENTAL DRUGS WILL NOT EXPAND ACCESS TO  
EXPERIMENTAL DRUGS FOR THE TERMINALLY ILL**

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*Desperate times call for desperate measures.*<sup>1</sup>

I. INTRODUCTION

In 2008, it was estimated that 565,650 Americans would die of cancer, accounting for one of every four deaths in the United States.<sup>2</sup> Doctors expected to diagnose 1,437,180 new patients with cancer throughout 2008, bringing the U.S. cancer population to over ten million.<sup>3</sup> While many of the cancers diagnosed are curable or manageable, others continue to remain deadly. These terminally ill patients are left desperate and willing to try just about anything regardless of the possibility of a cure or relief. Patients who believe they have nothing to lose have demanded faster turnaround of approval of drug treatment options, forcing the Food and Drug Administration (FDA) and the drug approval process into the spotlight. Particularly, these patients challenge the balance the government maintains between consumer protection and access to experimental treatments for terminally ill patients for whom no options exist. Some cancer organizations—representing members with personal and devastating stories about their loved ones’ struggle with cancer—have tried to sway the power away from the FDA by attempting to tip the balance between safety and efficacy in favor of providing the right of termi-

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<sup>1</sup> A translation of the Latin proverb “*extremis malis extrema remedia*” or “extreme remedies for extreme ills.”

<sup>2</sup> AMERICAN CANCER SOCIETY, CANCER FACTS & FIGURES 2008, at 2 (2008), available at <http://www.cancer.org/downloads/STT/2008CAFFfinalsecured.pdf>.

<sup>3</sup> *Id.* at 1.

nally ill patients to access experimental drugs. At the same time, a year of embarrassments involving such controversial medications as Vioxx has subjected the FDA to severe criticism about whether it is sufficiently protecting the public from dangerous drugs.<sup>4</sup> This clash of patient autonomy and consumer protection came to a head in a lawsuit filed by Abigail Alliance for Better Access to Developmental Drugs (Alliance), which sought access for the terminally ill to post-Phase I experimental drugs.

In August 2007, the United States Court of Appeals for the District of Columbia, sitting en banc, vacated the prior panel's decision in *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*, which decreed that terminally ill patients had a fundamental constitutional right to access experimental drugs that had only been through Phase I testing.<sup>5</sup> Prior to the en banc ruling, the panel had ruled that patients could have access to drugs tested solely for safety, with no evidence of efficacy.<sup>6</sup> In what appeared to be a huge defeat in increasing experimental intervention options for dying patients, Alliance was not deterred and filed a petition for writ of certiorari in the Supreme Court of the United States.<sup>7</sup>

In January 2008, the Supreme Court denied Alliance's petition for writ of certiorari refusing to weigh in on where the balance should be struck between patients' rights and consumer protection.<sup>8</sup> While Alliance considers its next move—to pursue its cause in an-

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<sup>4</sup> *Ensuring Drug Safety: Where Do We Go from Here: Hearing of the Comm. on Health, Educ., Labor, and Pensions*, 109th Cong. 3–4 (2005) (statement of Sen. Edward M. Kennedy).

<sup>5</sup> *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), *cert. denied*, 128 S. Ct. 1069 (2008). Numerous amicus curiae briefs were filed on behalf of both parties to the litigation. For the government, the following parties filed briefs: American Society of Clinical Oncology; National Coalition for Cancer Survivorship; Association of American Medical Colleges; National Organization for Rare Disorders; AIDS Action Baltimore; United Leukodystrophy Foundation; Neurofibromatosis, Inc.; Kennedy's Disease Association; National Ataxia Foundation; and the National Alopecia Areata Foundation. See D.C. Court of Appeals Docket, *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*, 495 F.3d 695 (D.C. Cir. 2007) (No. 04-5350). For Alliance, the following individuals filed briefs: economists including John Calfee, Daniel Klein, Sam Peltzman, Alex Tabarrok, and Benjamin Zycher; Dr. Emil Freireich from The University of Texas M.D. Anderson Cancer Center; and Dr. Stephen Strum. *Id.*

<sup>6</sup> *Abigail Alliance*, 445 F.3d at 486.

<sup>7</sup> *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*, 495 F.3d 695 (D.C. Cir. 2007) (en banc), *petition for cert. filed*, 76 U.S.L.W. 3373 (U.S. Sept. 28, 2008) (No. 07-444).

<sup>8</sup> *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*, 495 F.3d 695 (D.C. Cir. 2007) (en banc), *cert. denied*, 128 S. Ct. 1069 (2008).

other federal jurisdiction—the question left unanswered is whether all of this litigation will be productive in accomplishing Alliance’s goal of increasing access to experimental drugs. The gaping hole in Alliance’s strategy is how patients will obtain experimental drugs. Patients cannot compel pharmaceutical companies, which are non-state actors, to fulfill such a right. Therefore, Alliance presumably expects drug companies to voluntarily sell these experimental substances. However, this Comment proceeds on the presumption that drug companies will be unwilling to provide experimental drugs due to the cost, ethical concerns, practical infeasibilities, and potential tort claim liability.

This Comment proposes that the resources of the Court should not be consumed with deciding whether there is a fundamental right to access experimental drugs. Such a decision will prove futile because the result will not increase access to experimental drugs for the terminally ill. Ultimately, this Comment argues that the success of providing increased access to experimental drugs—regardless of changes implemented by Congress, the judiciary, or the FDA’s regulations—will depend on the participation of the drug companies; more specifically, success will depend on tailoring a program to offer adequate incentives to drug manufacturers while not sacrificing patients’ rights. Part II traces the history of the FDA drug approval process. Part III examines the Abigail Alliance organization and the procedural history of its litigation. Part IV evaluates the claim that Alliance’s litigation was and will continue to be futile because the pharmaceutical companies will remain unwilling to provide medication voluntarily in light of their legal, financial, and ethical constraints. Part V analyzes the proposed congressional legislation and FDA regulation addressing Alliance’s demands. Part VI suggests that the FDA’s regulatory proposal offers the most promising compromise for Alliance, provided the amendments can be adapted to include incentives for drug company participation in expanded access programs.

## II. HISTORY OF THE FDA APPROVAL PROCESS

### A. *Federal Food and Drug Act of 1906*

Drug-related public health problems evoked support for a uniform national regulation of the drug market, prompting Congress to

pass the Federal Food and Drug Act of 1906 (“1906 Act”).<sup>9</sup> The 1906 Act was aimed at banning both the manufacture and distribution of “adulterated and misbranded” drugs.<sup>10</sup> While the 1906 Act allowed the government to seize non-conforming drugs and prosecute offenders, the law was circumscribed in its focus to ensure that drugs adhered to a prescribed standard of strength, quality, or purity; and that a drug’s label accurately complied with the contents of the package.<sup>11</sup> Essentially, the 1906 Act centered on making misrepresentation illegal, which satisfy customer expectations by guaranteeing that drugs were what they claimed to be.<sup>12</sup> To this end, the 1906 Act was amended in 1912 to expand the notion of “misbranding” to also include false and misleading statements on labels as to the curative or remedial effects of drugs.<sup>13</sup> Importantly, the 1906 Act lacked any evaluation of the safety or effectiveness of new drugs entering the market.<sup>14</sup> The implications of this shortfall became apparent in 1937 when over 100 people died after ingesting a new antibiotic, Elixir Sulfanilamide, which unbeknownst to the public, was the equivalent of antifreeze.<sup>15</sup> In reaction to the public outcry over this tragedy, Congress passed the Food, Drug, and Cosmetic Act (FDCA) of 1938,<sup>16</sup>

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<sup>9</sup> Pure Food and Drugs Act of 1906, Pub. L. No. 59-384, 34 Stat. 768 (1906), *repealed by* Federal Food, Drug, and Cosmetic Act (FDCA), Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. § 301 (2000)); PETER HUTT ET AL., FOOD AND DRUG LAW 9 (3d ed. 2007). Uniform national regulation was strongly supported because the multitude of varying state statutes caused mischief, confusion, and embarrassment. HUTT, *supra*, at 9. A national tragedy—the distribution of tetanus infected diphtheria antitoxins which led to the death of several children—assisted in pushing the need for national regulation of the food and drug supply to the forefront of concerns. *Id.*

<sup>10</sup> Pure Food and Drugs Act of 1906, § 1. Under the 1906 Act, a drug was found adulterated when it differed from the established standard of strength, quality, or purity and if its strength or purity was below the professed standard or quality under which it was sold. *Id.* § 7. Additionally, according to the 1906 Act, a drug was misbranded if it was an imitation of a drug or offered for sale under the name of another drug, if the contents of the package had been removed and replaced with other drugs, or if the packaging failed to have a statement of the quantity of a long list of substances including alcohol, heroin, and chloroform. *Id.* § 8.

<sup>11</sup> *Id.* §§ 7–8, 11.

<sup>12</sup> *Id.* §§ 7–8.

<sup>13</sup> Pure Food and Drugs Act of 1906, *amended by* 37 Stat. 416 (1912). *See* United States v. Johnson, 221 U.S. 488 (1911) (holding that false and misleading statements on labels referring to curative or remedial effects of the drug were not considered misbranding under the 1906 Act).

<sup>14</sup> Pure Food and Drugs Act of 1906, §§ 1–13.

<sup>15</sup> PETER TEMIN, TAKING YOUR MEDICINE: DRUG REGULATION IN THE UNITED STATES 42–43 (1980).

<sup>16</sup> FDCA of 1938, Pub. L. No. 75-717, 52 Stat. 1040 (1932) (codified as amended at 21 U.S.C. § 301 (2000)).

which set the stage for modern-day drug regulation by shifting attention to the safety of drugs before distribution to the market.<sup>17</sup>

*B. Food, Drug, and Cosmetic Act of 1938*

Embarking on a new era of drug regulation, the FDCA required manufacturers of all “new drugs”<sup>18</sup> to file a new drug application (NDA) with the FDA including the appropriate scientific and medical data supporting the drug’s safety.<sup>19</sup> Once all information was filed, the FDA had sixty days to determine if the drug was unsafe.<sup>20</sup> If this deadline passed without any FDA contact, the drug was automatically “approved” for manufacturing and distribution.<sup>21</sup> If a manufacturer was put on notice by the FDA within the sixty-day time period, the FDA placed the new drug application on hold for up to 180 days in order to further study and investigate the drug and the application.<sup>22</sup> All applicants received an opportunity for a hearing with the FDA to establish the adequacy of their reports on the drug’s safety.<sup>23</sup> After such due process, the FDA suspended all applications which failed to effectively show the new drug was safe for distribution under the conditions of use upon which the application was based.<sup>24</sup> Hence, the 1938 version of the FDCA expanded the FDA’s ability to regulate new drug manufacturing and distribution based on safety.<sup>25</sup> However, the FDCA lacked a requirement for “affirmative” pre-market

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<sup>17</sup> *Id.*

<sup>18</sup> FDCA of 1938, Pub. L. No. 75-717, 52 Stat. 1040 (1932) (codified as amended at 21 U.S.C. § 321(p) (2000)). A “new drug” under the 1938 FDCA was defined as

Any drug . . . the composition of which is such that such drug is not generally recognized, among experts . . . as safe and effective for use under the conditions prescribed, recommended, or suggested . . . [or] any drug . . . the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

*Id.*

<sup>19</sup> FDCA of 1938, Pub. L. No. 75-717, 52 Stat. 1040 (1932) (codified as amended at 21 U.S.C. § 355(a)(1)(2000)). The FDCA of 1938 required that a full report of the investigations on a drug’s safety be submitted including a full list of the components of the drug, full description of the method used in manufacturing and packing the drug, and samples of the drug and the proposed labeling. *Id.*

<sup>20</sup> *Id.*

<sup>21</sup> *Id.*

<sup>22</sup> *Id.*

<sup>23</sup> *Id.*

<sup>24</sup> *Id.*

<sup>25</sup> FDCA of 1938, Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. § 355(a)(1)(2000)).

approval by the FDA for new drugs because NDAs were deemed approved after a sixty-day time period unless steps were taken to reject the application and prove the drug was dangerous.<sup>26</sup>

C. *Kefauver-Harris Amendments of 1962*

Congress dramatically revised the FDA approval process with the Kefauver-Harris Amendments of 1962 (“1962 Amendments”) to require that new drugs receive pre-market approval from the FDA based on safety and effectiveness.<sup>27</sup> The 1962 Amendments were triggered by America’s “close call” with the drug Thalidomide in the 1950s.<sup>28</sup>

1. The Thalidomide Tragedy

Thalidomide was developed in Germany and became widely used by the late 1950s in Europe as a morning sickness medication for pregnant women.<sup>29</sup> In September 1960, Richardson-Merrell Inc., which signed a contract to sell Thalidomide in the United States, applied for FDA approval of the new drug.<sup>30</sup> According to the FDCA of 1938, the FDA had only sixty days to review the company’s drug application before the drug would be automatically approved for distribution,<sup>31</sup> leaving plenty of time for Richardson-Merrell to meet its 1961 target distribution date.<sup>32</sup> A year and a half prior to Merrell’s submission of its NDA, the company began distributing Thalidomide for investigational use in clinical trials.<sup>33</sup> Merrell dispersed nearly 2,500,000 tablets to nearly 20,000 patients—including 624 pregnant women—while the drug was awaiting FDA approval.<sup>34</sup>

By the early 1960s, Thalidomide had been strongly linked to a rare birth defect in Europe called phocomelia—a shortening and de-

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<sup>26</sup> *Id.*

<sup>27</sup> Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified in scattered sections of 21 U.S.C. §§ 301–381 (2000)).

<sup>28</sup> 108 CONG. REC. H21058 (daily ed. Sept. 27, 1962) (statement of Rep. Sullivan acknowledging that without the media coverage on Thalidomide and Dr. Frances Kelsey from the FDA there might never have been any changes to the FDCA).

<sup>29</sup> Sue McGrath, *Only a Matter of Time: Lessons Unlearned at the Food and Drug Administration Keep Americans at Risk*, 60 FOOD DRUG L.J. 603, 606–07 (2005).

<sup>30</sup> *Id.*

<sup>31</sup> See *supra* text accompanying notes 20–22.

<sup>32</sup> McGrath, *supra* note 29, at 607.

<sup>33</sup> *Id.* at 608.

<sup>34</sup> Joseph Sanders, *The Bendectin Litigation: A Case Study in the Life Cycle of Mass Torts*, 43 HASTINGS L.J. 301, 314 (1992).

formity of the limbs resembling the extremities of a seal.<sup>35</sup> Mothers who had taken Thalidomide in West Germany bore between 3500 and 5000 babies afflicted with phocomelia in 1962 alone—prior to this, physicians rarely diagnosed a single case in an entire career.<sup>36</sup> Fortunately and largely by chance, the United States, in comparison to many parts of the world where Thalidomide had been distributed, largely escaped this tragedy due to Dr. Frances Kelsey at the FDA.<sup>37</sup> After reviewing Merrell's application, Dr. Kelsey found deficiencies in its studies and on the fifty-eighth day, two days before the drug would have been automatically approved for sale, placed the Thalidomide application on hold.<sup>38</sup> The application was subsequently postponed numerous times, and in March 1962 Merrell withdrew its application.<sup>39</sup> All in all, Thalidomide caused 10,000 children in forty-six countries to be born with deformities; only seventeen were born in America.<sup>40</sup>

## 2. The Aftermath of Thalidomide: The Passage of the 1962 Amendments

While prior attempts to reform the 1938 FDCA had been unsuccessful, the “close call” with Thalidomide forced the government to re-evaluate the drug approval process and specifically to examine the FDA's limited authority to prevent pervasive use of an unproven, insidious drug.<sup>41</sup> Hence, Congress enacted the 1962 Amendments and replaced the pre-market notification system with *pre-market approval* both for safety *and* effectiveness for all new drugs.<sup>42</sup> These changes converted the FDA's role to a proactive participant acting as a consumer protection watchdog in the drug approval process.<sup>43</sup>

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<sup>35</sup> 108 CONG. REC. H21058–59 (daily ed. Sept. 27, 1962) (statement of Rep. Sullivan quoting a report from the Associated Press).

<sup>36</sup> *Id.*

<sup>37</sup> *Id.* at 21072 (statement of Rep. Yates).

<sup>38</sup> McGrath, *supra* note 29, at 608; Linda Bren, *Frances Oldham Kelsey: FDA Medical Reviewer Leaves Her Mark on History*, FDA CONSUMER MAG., Mar.–Apr. 2001, at 24, available at [http://www.fda.gov/fdac/features/2001/201\\_kelsey.html](http://www.fda.gov/fdac/features/2001/201_kelsey.html) (last visited Sept. 2, 2008).

<sup>39</sup> McGrath, *supra* note 29, at 608.

<sup>40</sup> Bren, *supra* note 38.

<sup>41</sup> See 108 CONG. REC. H21070 (daily ed. Sept. 27, 1962) (statement of Rep. Reuss).

<sup>42</sup> Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified in scattered sections of 21 U.S.C. §§ 301–381(2000)); see 108 CONG. REC. H21058–73 (daily ed. Sept. 27, 1962).

<sup>43</sup> See TEMIN, *supra* note 15, at 125.

The 1962 Amendments control today's drug approval process. Manufacturers must obtain pre-market FDA approval by submitting for review to the FDA sufficient evidence of safety and effectiveness of any new drug.<sup>44</sup> The FDA also exercises authority over new drug pre-approval events, especially clinical trials involving humans.<sup>45</sup> Additionally, the FDA has post-market jurisdiction over safety, advertisements, and promotions.<sup>46</sup>

#### D. Current Drug Approval Procedure

The process for drug approval is complicated, time-consuming, and expensive. Before even submitting a new drug application, a manufacturer must conduct clinical studies designed to show the drug is both safe and effective.<sup>47</sup> The process begins with an investigational new drug (IND) application to commence clinical testing on humans.<sup>48</sup> These IND applications generally follow pre-clinical testing on animals to get initial projections on safety that takes about 3.5 years.<sup>49</sup> Pre-approval testing on humans involves three separate phases of investigative studies.<sup>50</sup>

##### 1. Phase I Testing

Phase I testing entails the initial introduction of the experimental drug in humans<sup>51</sup> and usually lasts about a year,<sup>52</sup> involving between twenty and eighty healthy volunteers.<sup>53</sup> The studies seek "to determine the metabolism and pharmacologic actions of the drugs in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence of effectiveness."<sup>54</sup> Essentially, Phase I tests are designed to study metabolism and toxicity, but these tests provide only preliminary information on safety and possibly no information regarding efficacy.<sup>55</sup> It is important not to accord more

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<sup>44</sup> 21 U.S.C. § 355(b)(1) (2000).

<sup>45</sup> *Id.* § 355(b)(5).

<sup>46</sup> *See id.* § 355(e), § 352(n); 21 C.F.R. 202.1 (2007).

<sup>47</sup> 21 U.S.C. § 355(b).

<sup>48</sup> *Id.*

<sup>49</sup> Elizabeth M. Rutherford, *The FDA and "Privatization"—The Drug Approval Process*, 50 FOOD & DRUG L.J. 203, 212 (1995).

<sup>50</sup> 21 C.F.R. § 312.21 (2007).

<sup>51</sup> *Id.* § 312.21(a)(1).

<sup>52</sup> Rutherford, *supra* note 49, at 213.

<sup>53</sup> 21 C.F.R. § 312.21(a)(1).

<sup>54</sup> *Id.*

<sup>55</sup> Susan Okie, *Access Before Approval—A Right to Take Experimental Drugs?*, 355 NEW ENG. J. MED. 437, 438 (2006).



weight than is appropriate to the results of a Phase I study; Phase I studies are basically assuring that a new drug does not poison a subject.<sup>56</sup> Phase I is usually the safest phase for human testing because it involves healthy volunteer subjects, low doses, and close medical supervision.<sup>57</sup> However, disasters do happen. Recent Phase I trials resulted in one death and six serious adverse effects.<sup>58</sup> The Center for Drug Evaluation and Research (CDER), which oversees testing under the FDCA, can place a study on a clinical hold if it has concerns over safety or a sponsor's insufficient risk disclosure.<sup>59</sup>

## 2. Phase II Testing

Phase II testing increases the controlled trial group to several hundred subjects and is meant to evaluate "the effectiveness of the drug for a particular indication in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug."<sup>60</sup> Phase II clinics can last about two years.<sup>61</sup> The FDA requires that these trials be adequate and well controlled studies which allow identification of the effects of the drug to be shown from other influences other than the specific chemicals that are being tested.<sup>62</sup> As such, most clinical trials involve comparisons to control groups that receive placebos or the current best treatment, randomized assignment to treatment, and blinded outcome assessment.<sup>63</sup> Because study participants have the possibility of either unknowingly receiving the experimental drug or a placebo, and because the drug being tested has not yet been proven effective,<sup>64</sup> a critical distinction for all participants in clinical trials must be

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<sup>56</sup> Rita Rubin, *Unapproved Drugs Ignite Life-and-Death Debate; Lawsuit Pits Desperately Ill Against Hard Bureaucratic Realities*, USA TODAY, Apr. 2, 2007, at 1A (quoting Bioethicist Arthur Caplan from the University of Pennsylvania).

<sup>57</sup> 21 C.F.R. § 312.21(a)(1).

<sup>58</sup> See generally S.E. Raper et al., *Fatal Systemic Inflammatory Response Syndrome in an Orinithine Transcarbamylase Deficient Patient Following Adenoviral Gene Transfer*, 80 MOLECULAR GENETICS METABOLISM 148 (2003) (discussing the death of Jesse Gelsinger); Ganesh Suntharalingam et al., *Cytokine Storm in a Phase I Trial of the Anti-CD28 Monoclonal Antibody TGN1412*, 355 NEW ENG. J. MED. 1018 (2006) (serious adverse reactions on six healthy patients).

<sup>59</sup> The CDER Handbook, *The New Development and Review Process: Phase I Clinical Studies*, <http://www.fda.gov/cder/handbook/phase1.htm> (last visited Sept. 3, 2008).

<sup>60</sup> 21 C.F.R. § 312.21(b).

<sup>61</sup> Rutherford, *supra* note 49, at 213.

<sup>62</sup> P.P. De Deyn & R. D'Hooge, *Placebos in Clinical Practice and Research*, 22 J. MED. ETHICS 140, 140-41 (1996).

<sup>63</sup> *Id.*

<sup>64</sup> *Id.*

made indicating that their involvement in the trial is not experimental therapy but an experimental study.<sup>65</sup> Phase II studies are not meant to treat but are intended solely to evaluate whether the substances at issue offer therapeutic benefits.<sup>66</sup> Physicians must follow protocol, from which they may not deviate even if they believe it is in the participant's best medical interest.<sup>67</sup> Participants are consequently referred to as subjects instead of patients to solidify this distinction.<sup>68</sup> However, despite this distinction, most subjects are motivated to join clinical trials due to the recruitment efforts of their physician,<sup>69</sup> hope for personal benefit, and lack of alternative options for their own treatment.<sup>70</sup>

To become a participant in Phase II trials, patients must satisfy specific eligibility criteria.<sup>71</sup> These may include a particular age, gender, medical history, current health status, and type or stage of disease.<sup>72</sup> These initial trials do not involve participation by minors; however, the FDA mandates that sponsors must incorporate children in testing if the drug is specifically marketed for children.<sup>73</sup> Additionally, clinical trials usually take place at cancer centers, medical centers, community hospitals, specialized centers, and doctors' offices,<sup>74</sup> possibly requiring subjects to travel great lengths to participate. All research involving human subjects is governed by federal

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<sup>65</sup> Frances H. Miller, *Symposium Trust Relationships Part 1 of 2: Trusting Doctors: Tricky Business When It Comes to Clinical Research*, 81 B.U. L. REV. 423, 433 (2001).

<sup>66</sup> *Id.*

<sup>67</sup> *Id.*

<sup>68</sup> *Id.*

<sup>69</sup> There exists the possibility for a conflict of interest between a physician and his referral to his patient to enter a clinical study when the physician is being compensated by a sponsor with the receipt of "finder's fees." Jesse A. Goldner, *Dealing with Conflicts of Interest in Biomedical Research: IRB Oversight as the Next Best Solution to the Abolitionist Approach*, 28 J. L. MED. & ETHICS 379, 381-82 (2000). Additionally, a recent trend in clinical research has been the shift from research of investigators at academic medical centers to private physicians running and directing research as a physician-investigator. Jason E. Klein & Alan R. Fleischman, *The Private Practicing Physician-Investigator: Ethical Implications of Clinical Research in the Office Setting*, 32 HASTING CTR. RPT., July-Aug. 2002, at 22-24. This new dual role of physicians creates conflicts of interests between the physician and his patients when sponsors are compensating the physician to recruit, retain, and study research subjects. *Id.*

<sup>70</sup> Nancy Kass et al., *Trust: The Fragile Foundation of Contemporary Biomedical Research*, 26 HASTING CTR. REP. 25, 26 (1996).

<sup>71</sup> Nat'l Cancer Inst., *Clinical Trials Questions and Answers*, <http://www.cancer.gov/cancertopics/factsheet/Information/clinical-trials> (last visited Sept. 12, 2008).

<sup>72</sup> *Id.*

<sup>73</sup> 21 C.F.R. § 201.57 (2007).

<sup>74</sup> Nat'l Cancer Inst., *supra* note 71.

law and is subject to Institutional Board Review<sup>75</sup> (IRB) approval.<sup>76</sup> IRBs perform the initial review of the clinical research program—including approval of research protocol, informed consent, and advertisements—and oversee the clinical trial in progress to evaluate the on-going degree of risk.<sup>77</sup>

### 3. Phase III Testing

Phase III testing attempts “to gather information about effectiveness and safety needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling.”<sup>78</sup> The size of the group is drastically expanded to several hundred or several thousand subjects.<sup>79</sup> Phase III includes both controlled and uncontrolled testing.<sup>80</sup> This means subjects in a Phase III trial could be subject to two scenarios: a controlled setting, where there is a possibility of receiving the experimental drug or placebo, or an uncontrolled setting, where all subjects receive the experimental drug and there is no comparison control group.<sup>81</sup> While randomized, controlled trials are considered the gold standard in drug evaluation,<sup>82</sup> the allowance of both types of studies permits broader participation in the trial. Many cancer subjects cite the trial’s design and use of randomized placebo control groups as the main reason for refusal to participate in the study.<sup>83</sup> Similarly to Phase II, subjects must meet certain qualifications to participate.<sup>84</sup> Phase III testing lasts about three years.<sup>85</sup>

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<sup>75</sup> Institutional Review Boards are required to have at least five members with varying backgrounds and diversity. 45 C.F.R. § 46.107 (2007). To form an adequate IRB, at least one member must have primary scientific concerns, at least one member must have primary non-scientific concerns, and at least one member must not be affiliated with the institution. *Id.* No IRB member may have a conflict of interests in reviewing a sponsor’s program. *Id.* In order to gain approval from an IRB, a quorum is needed to vote which includes at least one member whose primary concern is not in a scientific area. 45 C.F.R. § 46.108 (2007).

<sup>76</sup> 45 C.F.R. §§ 46.101, 46.109 (2007).

<sup>77</sup> 45 C.F.R. § 46.109.

<sup>78</sup> 21 C.F.R. § 312.21(c) (2007).

<sup>79</sup> *Id.*

<sup>80</sup> *Id.*

<sup>81</sup> De Deyn & D’Hooge, *supra* note 62, at 140–42.

<sup>82</sup> Katie Featherstone & Jenny L. Donovan, “Why Don’t They Just Tell Me Straight, Why Allocate It?” *The Struggle To Make Sense of Participating in Randomised Controlled Trial*, 55 SOC. SCI. & MED. 709, 709 (2002).

<sup>83</sup> Priscilla Alderson, *Equipose as a Means of Managing Uncertainty: Personal, Communal and Proxy*, 22 J. MED. ETHICS 135, 138 (1996).

<sup>84</sup> See *supra* text accompanying note 72.

<sup>85</sup> Rutherford, *supra* note 49, at 213.

#### 4. Post-Phase Testing Procedure

At the completion of all testing phases, the pharmaceutical company must file the NDA with the FDA for drug marketing approval.<sup>86</sup> This application must contain reports of the sponsor's investigations of the drug product and sufficient information about the drug which the sponsor believes is pertinent to the evaluation of the application.<sup>87</sup> The FDA maintains specific guidance documents on the format and content of the applications.<sup>88</sup> All data and information on safety and effectiveness submitted in an application may be disclosed to the public upon request unless the FDA finds that extraordinary circumstances exist.<sup>89</sup>

While the FDCA provides the FDA with 180 days to act on the NDA,<sup>90</sup> taking into account delays and informational requests, the FDA averages thirty months to review a NDA.<sup>91</sup> All things considered, the entire drug approval process averages twelve years.<sup>92</sup> Only about eleven percent of drugs evaluated in Phase I—and only six percent of cancer drugs—ultimately are approved by the FDA; the others either prove too toxic or do not work.<sup>93</sup> Drug companies pay for the cost of all clinical trials, and by the time a potential new drug reaches the market, drug companies claim the product has cost nearly a billion dollars in development.<sup>94</sup> However, pharmaceutical companies' figures for cost of development have been disputed on the grounds that their calculations are inflated to justify charging higher prices and that in the end industry profits far exceed the costs of development.<sup>95</sup>

#### E. Exceptions to Current Approval Procedure

FDA programs for expanded access to medical treatment originated out of the AIDS epidemic in the late 1980s and early 1990s. By

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<sup>86</sup> 21 C.F.R. § 314.50 (2007).

<sup>87</sup> *Id.*; 21 U.S.C. § 355(b) (2000); *see* Rutherford, *supra* note 49, at 213 (noting that supporting information may contain over 100,000 pages of documentation).

<sup>88</sup> 21 C.F.R. § 314.50.

<sup>89</sup> 21 U.S.C. § 355(i)(1).

<sup>90</sup> *Id.* § 355(c)(1).

<sup>91</sup> Rutherford, *supra* note 49, at 213.

<sup>92</sup> *Id.*

<sup>93</sup> Okie, *supra* note 55, at 439.

<sup>94</sup> Joseph DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 181 (2003).

<sup>95</sup> MARCIA ANGELL, THE TRUTH ABOUT DRUG COMPANIES: HOW THEY DECEIVE US AND WHAT TO DO ABOUT IT 1, 51 (2004). Angell suggests that included in the cost of research and development are the cost of marketing activities. *Id.* at 156–172. *Compare* RICHARD EPSTEIN, OVERDOSE: HOW EXCESSIVE GOVERNMENT REGULATION STIFLES PHARMACEUTICAL INNOVATION 1, 165 (Yale Univ. Press 2006).

this time, AIDS had contributed to over 200,000 deaths in the United States and remained one of the leading causes of death among middle aged men and women.<sup>96</sup> The gravity and speed of this epidemic, along with its strong advocacy organizations, pressured the FDA to expedite access to experimental drugs for what was then a terminal, rather than chronic, disease.<sup>97</sup> The FDA implemented two main policy changes: the compassionate-use programs for investigational new drugs and the fast-track program.

### 1. Compassionate-Use Program

Acknowledging the lengthy timeframe of the drug approval process, the FDA has created compassionate-use provisions to expedite access<sup>98</sup> to promising new drugs to terminally ill patients who do not qualify for clinical trials.<sup>99</sup> To qualify for the compassionate-use exception, the following criteria must be met: (1) the drug must be “intended to treat a serious or immediately life-threatening illness”;<sup>100</sup> (2) there must be “no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population”;<sup>101</sup> (3) the drug must be “under investigation in a controlled clinical trial under an IND in effect for the trial,” or all clinical trials must have been completed;<sup>102</sup> and (4) the sponsor of the controlled clinical trial must be “actively pursuing marketing approval of the investigational drug.”<sup>103</sup> Hence, availability of the exception depends on the type of illness and stage of the drug approval process.

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<sup>96</sup> Anne Rochell, *AIDS Deaths in U.S. Top 200,000*, ATLANTA CONSTITUTION, Oct. 29, 1993, at A1; see also Richard Selik et al., *HIV Infection as Leading Cause of Death Among Young Adults in U.S. Cities and States*, 270 JAMA 2991, 2992 (1993) (total U.S. deaths attributable to AIDS is 143,653 in 1990).

<sup>97</sup> Philip J. Hiltz, *How the AIDS Crisis Made Drug Regulators Speed Up*, N.Y. TIMES, Sept. 24, 1989, at D5.

<sup>98</sup> See Jerome Groopman, *The Right to Trial; Should Dying Patients Have Access to Experimental Drugs?*, NEW YORKER, Dec. 18, 2006, at 40, 46, for an example of the compassionate-use provision in practice. The drug Iressa was given to 24,000 lung-cancer patients while still an experimental drug after a Phase II trial showed promising results. *Id.* Unfortunately, Iressa was never approved by the FDA when subjects failed to show improvements in Phase III clinical trials. *Id.*

<sup>99</sup> 21 C.F.R. § 312.34(a) (2008).

<sup>100</sup> *Id.* § 312.34(b)(1)(i).

<sup>101</sup> *Id.* § 312.34(b)(1)(ii); see also Groopman, *supra* note 98, at 46 (explaining one instance where a patient was denied use of an experimental brain tumor drug because the patient had refused to undergo radiation therapy which is the standard treatment for the condition).

<sup>102</sup> 21 C.F.R. § 312.34(b)(1)(iii).

<sup>103</sup> *Id.* § 312.34(b)(1)(iv).

Erring on the side of consumer protection, even expedited access is administered conservatively. Drugs will most likely be made available only in Phase III of the process or if all clinical trials have been completed.<sup>104</sup> In appropriate and rare circumstances, a drug may be made available prior to Phase III, but never earlier than post-Phase II; however, this allowance is only warranted with an immediate life-threatening disease when all treatment options have been exhausted.<sup>105</sup> The FDA Commissioner retains the discretion to deny a request for compassionate-use.<sup>106</sup> This discretion may be employed if the available scientific evidence fails to show the drug is effective for its intended use or provides reasonable grounds which indicate the patient would be exposed to an unreasonable and significant additional risk of illness.<sup>107</sup>

The law prohibits the drug sponsor from profiting on compassionate-use of experimental drugs, restricting recovery to the cost of manufacture, research, development, and handling of investigational drugs.<sup>108</sup> Thus, pharmaceutical companies have little motivation to comply with drug requests from expanded use programs and many have refused involvement, fearing that compassionate-use programs will interfere with clinical trials and ultimately negatively impact drug approval.<sup>109</sup>

## 2. Fast-Track Program

The FDA designed the fast-track program to facilitate development and expedite review of new drugs for serious illnesses.<sup>110</sup> To this end, the program encourages early and ongoing consultation and communication between the FDA and the drug companies—both before clinical testing on humans and after Phase I testing—to improve the efficiency of the process.<sup>111</sup> Under the fast-track provisions, the FDA may approve drugs after Phase II if results appear promising.<sup>112</sup> FDA approval is based on the agency making a medical risk-benefit judgment considering the availability of other therapies

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<sup>104</sup> *Id.* § 312.34(a).

<sup>105</sup> *Id.* § 312.34(a).

<sup>106</sup> *Id.* § 312.34(b)(3)(i)(A)–(B).

<sup>107</sup> *Id.*

<sup>108</sup> 21 C.F.R. § 312.7(d)(3) (2008).

<sup>109</sup> Groopman, *supra* note 98, at 45–46, 47.

<sup>110</sup> Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended to Treat Life-Threatening and Debilitating Illnesses, 53 Fed. Reg. 41,515, 41,516 (1988) (codified at 21 C.F.R. §§ 312, 314).

<sup>111</sup> 21 C.F.R. § 312.82 (2008).

<sup>112</sup> *Id.* § 312.83.

and the severity of the disease.<sup>113</sup> Finally, if approval is granted, the FDA may require the sponsor to conduct post-marketing, Phase IV, studies to evaluate further the drug's risks, benefits, and optimal uses.<sup>114</sup>

As a result of the fast-track program, the drug zidovudine, AZT, was the first drug approved to treat the AIDS virus, and in record time.<sup>115</sup> Approval of treatment protocol took five days and marketing approval post-Phase II took only 107 days due to well-controlled and well-executed clinical trials.<sup>116</sup> The total drug approval time was shortened from eight years to two years.<sup>117</sup> Additionally, under the compassionate-use program, AZT, during its development, was distributed to more than 4000 patients while the marketing application was being pulled together by the sponsor and reviewed by the FDA.<sup>118</sup>

Despite this success, the reaction to promoting early and wider access to experimental drugs was mixed, especially within the AIDS community. Some researchers feared that earlier availability of drugs, without full testing on safety and efficacy, was risky and detrimental to patients and the pursuit of a cure.<sup>119</sup> The pharmaceutical companies were equally unenthusiastic about the expanded use programs, arguing that drugs needed to be further tested before applying for an IND.<sup>120</sup> Following the first year of the program, the expanded access programs were labeled a "failure" and a "sham" for their inability to facilitate any potential drugs to attack AIDS directly.<sup>121</sup> Only one sponsor had applied for and received approval for a treatment IND for a HIV-related drug.<sup>122</sup> Even though physicians

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<sup>113</sup> Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended to Treat Life-Threatening and Debilitating Illnesses, 53 Fed. Reg. at 41,523; 21 C.F.R. § 312.84.

<sup>114</sup> Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended to Treat Life-Threatening and Debilitating Illnesses, 53 Fed. Reg. at 41,517; 21 C.F.R. § 312.85.

<sup>115</sup> Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended to Treat Life-Threatening and Debilitating Illnesses, 53 Fed. Reg. at 41,519.

<sup>116</sup> *Id.*

<sup>117</sup> *Id.*

<sup>118</sup> *Id.* at 41,520.

<sup>119</sup> Hilts, *supra* note 97, at D5.

<sup>120</sup> Philip Boffey, *New Initiative to Speed AIDS Drugs Is Assailed*, N.Y. TIMES, July 5, 1988, at C1.

<sup>121</sup> PRESIDENTIAL COMM'N ON THE HUMAN IMMUNODEFICIENCY VIRUS EPIDEMIC, REPORT OF THE PRESIDENTIAL COMMISSION ON THE HUMAN IMMUNODEFICIENCY VIRUS EPIDEMIC 50 (1988) [hereinafter PRESIDENTIAL COMM'N REPORT]; Boffey, *supra* note 120, at C1.

<sup>122</sup> PRESIDENTIAL COMM'N REPORT, *supra* note 121, at 50.

and the terminally ill sought medication, pharmaceutical companies hesitated to release their drugs.<sup>123</sup> Drug companies' lack of participation in the programs stemmed from their concern about disruptions in their clinical trials, as well as fear of increased susceptibility to liability suits.<sup>124</sup>

III. *ABIGAIL ALLIANCE FOR BETTER ACCESS TO DEVELOPMENT DRUGS V. VON ESCHENBACH*

A. *Formation of Abigail Alliance for Better Access to Development Drugs*

Alliance is a non-profit organization consisting of terminally ill patients and their supporters whose main mission is to "help cancer patients and others with life threatening illnesses."<sup>125</sup> Frank Burroughs founded Alliance in 2001, naming the foundation after his daughter, Abigail, who lost her life to terminal cancer.<sup>126</sup> Prior to her death, Abigail had exhausted all of the FDA-approved treatment options available.<sup>127</sup> Her physician was encouraged by a new unapproved drug which he believed showed a good response in early clinical trials, and he recommended experimenting with such usage.<sup>128</sup> Abigail did not qualify for the clinical trials of the new drug, and the drug company could not provide her with the drug through the compassionate-use program.<sup>129</sup> In her memory, Alliance has sought to assist terminally ill patients in gaining access to experimental drugs before efficacy has been shown in clinical trials by lobbying for con-

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<sup>123</sup> *Id.*

<sup>124</sup> Boffey, *supra* note 119, at C1.

<sup>125</sup> Abigail Alliance for Access to Development Drugs, The Abigail Alliance Mission, <http://abigail-alliance.org/mission.htm> (last visited Sept. 12, 2008).

<sup>126</sup> Sue Kovach, *The Abigail Alliance: Motivated by Tragic Circumstances, Families Battle an Uncaring Bureaucracy*, LIFE EXTENSION, Sept. 2007, at 25, available at <http://abigail-alliance.org/LEMSEP07pAbigailLR.pdf>.

<sup>127</sup> *Id.*

<sup>128</sup> *Id.* at 26.

<sup>129</sup> *Id.* Abigail Burroughs was seeking access to the drug Erbitux, manufactured by ImClone Systems. *Id.* ImClone filed their original request for approval at the FDA in 2001; however, the FDA determined that the application could not be reviewed since the clinical data was inadequate: "half of the patients studied had not failed the approved treatments for colon cancer and important information about safety and effectiveness of Erbitux in a portion of the remaining patients was missing." Press Release, FDA, FDA Approves Erbitux for Colorectal Cancer (Feb. 12, 2004) (available at <http://www.fda.gov/bbs/topics/NEWS/2004/NEW01024.html>). In 2003, ImClone resubmitted results from a well-run trial and supplemented missing information from their original 2001 request. *Id.* The FDA approved Erbitux on February 12, 2004. *Id.*



gressional change, protesting the FDA, encouraging cooperation with drug companies, and educating the public on the need to increase access to potential life-saving drugs.<sup>130</sup>

### 1. Procedural History

In furtherance of its mission, Alliance submitted a proposal to the FDA in January 2003 for new regulations that would make experimental drugs available after Phase I trials to terminally ill patients who were not selected for clinical trials.<sup>131</sup> In so doing, Alliance attempted to expand the FDA's extant compassionate-use program that allows investigational drugs to be accessed after Phase III, and with some exceptions, after Phase II.<sup>132</sup> The FDA rejected Alliance's petition, concluding that the proposal would upset the appropriate balance the FDA sought to maintain.<sup>133</sup> The FDA noted that "in the realm of reviewing medical products to treat serious and life-threatening diseases, there is inevitable tension between early availability of products to patients, especially patients with refractory disease,<sup>134</sup> and the need to obtain sufficient data to provide a reasonable expectation of benefit and lack of excessive harm."<sup>135</sup> Accordingly, the FDA concluded that increasing patient availability before a risk-benefit analysis could be performed would be detrimental.<sup>136</sup>

Such a response was unsurprising considering the context in which the FDA reviewed Alliance's proposal. In 2003, product liability lawsuits were filed against Merck because of the dangerous side-effects of the drug Vioxx, subjecting the FDA to enormous criticism for allowing an unsafe product to the market.<sup>137</sup> The FDA approved Vioxx in 1999 for treatment of pain and inflammation associated with arthritis.<sup>138</sup> However, after being on the market for a few years, Vioxx

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<sup>130</sup> Kovach, *supra* note 126, at 29.

<sup>131</sup> *Abigail Alliance for Better Access to Developmental Drugs v. McClellan*, No. 03-1601, 2004 U.S. Dist. LEXIS 29594, at \*\*3-4 (D.D.C. Aug. 30, 2004).

<sup>132</sup> See *supra* notes 89-96.

<sup>133</sup> *Abigail Alliance*, 2004 U.S. Dist. LEXIS 29594, at \*4.

<sup>134</sup> A refractory disease is defined as a disease which is obstinate or not readily yielding to treatment. *STEDMAN'S MEDICAL DICTIONARY* 1542 (28th ed. 2005).

<sup>135</sup> *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*, 445 F.3d 470, 490 (D.C. Cir. 2006).

<sup>136</sup> *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*, 495 F.3d 695, 700 (D.C. Cir. 2007).

<sup>137</sup> Alex Berenson, *Merck Asks for a Dismissal in First of Suits over Vioxx*, N.Y. TIMES, Apr. 13, 2005, at C5; Walter T. Champion, *The Vioxx Litigation Paradigm: The Search for Smoking Guns*, 31 T. MARSHALL L. REV. 157, 167, 173 (2006).

<sup>138</sup> Champion, *supra* note 137, at 158, 163-64.

was shown to cause adverse cardiovascular side effects.<sup>139</sup> While Merck pulled Vioxx from distribution in 2004, skepticism increased as to how such a dangerous drug could reach the market, leaving questions about the state and effectiveness of clinical trials.<sup>140</sup> Ironically, Alliance's timing for promoting early access to experimental drugs coincided with a movement that focused on promoting the safety of drugs over increasing the speed by which drugs entered the market.

It was against this background that Alliance filed a citizen petition,<sup>141</sup> pursuant to 21 C.F.R. § 10.30, challenging the FDA's policy prohibiting the distribution of experimental drugs to terminally ill patients.<sup>142</sup> The FDA acknowledged but did not respond to the petition, which allowed Alliance the right to judicial review.<sup>143</sup> Consequently, Alliance filed suit against the FDA Commissioner and the Secretary of the Department of Health and Human Services to enjoin the FDA from forbidding the sale and distribution of post-Phase I experimental drugs.<sup>144</sup> The U.S. District Court for the District of Columbia dismissed the complaint for failure to state a claim because Alliance was seeking to establish a new constitutional right to life not explicitly granted in the due process clause.<sup>145</sup> The court acknowledged the nation's focus on preserving life but did not accept Alliance's argument that the Supreme Court's recognition of the right to refuse life-saving medical treatment<sup>146</sup> created a "complementary right to choose life by obtaining potentially life-saving medication."<sup>147</sup> Without an established fundamental due process right, the court examined Alliance's claims under rational basis review and held that the FDA's policy on restricting access to unapproved drugs is ration-

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<sup>139</sup> *Id.* at 164.

<sup>140</sup> *Id.* at 166–67.

<sup>141</sup> A Citizen Petition is a means for interested parties to initiate administrative proceedings in order to petition the Commissioner of the FDA to issue, amend, or revoke a regulation or refrain from taking a certain action. 21 C.F.R. § 10.25(a) (2008). The format and contents of the petition are governed the rules set out in 21 C.F.R. § 10.30 (2008). The Commissioner of the FDA has the authority to grant or deny petitions and must respond to each petitioner within 180 days of receipt. *Id.* § 10.30(e)(1)–(3).

<sup>142</sup> *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*, 445 F.3d 470, 473 (D.C. Cir. 2006).

<sup>143</sup> *Id.*

<sup>144</sup> *Id.* at 473–74.

<sup>145</sup> *Id.* at 474.

<sup>146</sup> See *Cruzan v. Dir. Missouri Dept. of Health*, 497 U.S. 261 (1990) (upholding the legal principle that individuals have a right to refuse medical treatment).

<sup>147</sup> *Abigail Alliance*, 445 F.3d at 474–75.

ally related to the legitimate governmental interest of protecting public health.<sup>148</sup>

Alliance appealed this dismissal and in May 2006 the U.S. Court of Appeals for the District of Columbia Circuit reviewed the motion to dismiss de novo.<sup>149</sup> On appeal, the issue was whether fundamental due process rights to privacy, liberty, and life include the right of terminally ill patients who are informed and acting on their doctor's advice to obtain potentially life-saving, unapproved drugs when no alternative exists.<sup>150</sup> In a two-to-one decision, the court overturned the district court's dismissal for failure to state a claim, holding that due process protects the rights of terminally ill patients to have access to post-Phase I investigational drugs.<sup>151</sup> In arriving at this decision, the court based its analysis on whether such a right was part of our nation's "history and legal tradition" and "implicit in the concept of liberty."<sup>152</sup>

The court created a careful and narrow description of the fundamental right: "the right of terminally ill patients, acting on a doctor's advice, to obtain potentially life-saving medication when no alternative treatment approved by the government is available."<sup>153</sup> The court looked to three common law doctrines to show a right to self-preservation in our nation's history and legal tradition—the doctrine of necessity, the tort of intentional interference with rescue, and the right to self-defense.<sup>154</sup> The court recognized in Anglo-American history a tradition that "when a person is faced with death, necessity often warrants extraordinary measures not otherwise justified."<sup>155</sup> Denying patients access to life-saving drugs, then, would violate this right of self-preservation.<sup>156</sup> Additionally, the court examined the history of drug regulation, concluding that regulating access to new drugs was recent in our nation's history.<sup>157</sup> The court supported its position of allowing access by stating that restricting access was not part of America's tradition, since drugs were not regulated until 1906 and it was

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<sup>148</sup> *Id.* at 475.

<sup>149</sup> *Id.*

<sup>150</sup> *Id.* at 477–78.

<sup>151</sup> *Id.* at 486.

<sup>152</sup> *Id.* at 476–77.

<sup>153</sup> *Abigail Alliance*, 445 F.3d at 478.

<sup>154</sup> *Id.* at 480–81.

<sup>155</sup> *Id.* at 480.

<sup>156</sup> *Id.*

<sup>157</sup> *Id.* at 481.

not until 1962 that access to new drugs required a showing of efficacy.<sup>158</sup>

The court not only found the right to experimental drugs established in our nation's history and legal tradition but concluded that such a right was "implicit in the concept of ordered liberty."<sup>159</sup> The court held that the right to access unapproved drugs was implied in the Court's decision in *Cruzan v. Missouri Department of Health*, which held that the due process clause protects a person's right to refuse life-saving medical treatment.<sup>160</sup> The court noted that this holding created a due process right to "make an informed decision to engage in conduct, by withdrawing treatment, that will cause one's death."<sup>161</sup> Applying the due process rights established in *Cruzan* to Alliance's case, the court found that the "logical corollary is that an individual must also be free to decide for herself whether to assume any known or unknown risks of taking a medication that might prolong her life."<sup>162</sup> The court remanded the case to the district court to determine whether the FDA's policy would pass strict scrutiny.<sup>163</sup>

On March 1, 2007, the FDA appealed the decision of the U.S. Court of Appeals for the District of Columbia and the court agreed to hear the case en banc.<sup>164</sup> By August 2007, the court of appeals vacated its prior decision in an eight-to-two vote concluding "that there is no fundamental right 'deeply rooted in this Nation's history and tradition' of access to experimental drugs for the terminally ill."<sup>165</sup> In order for Alliance to succeed on its claim, the court found it needed to show that there was both a tradition of access to drugs that have not been proven effective and a tradition of access to drugs that have not been proven safe.<sup>166</sup> It was not adequate only to show that the government did not have a long history of regulating drugs in a general sense.<sup>167</sup> In its analysis, the court examined the history of drug regulation since 1736 and concluded that Alliance had ignored the nation's history of drug safety regulation prior to governmental acts

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<sup>158</sup> *Id.* at 481–82.

<sup>159</sup> *Abigail Alliance*, 445 F.3d at 483–84 (quoting *Palko v. Connecticut*, 302 U.S. 319, 325 (1937)).

<sup>160</sup> *Id.* at 484.

<sup>161</sup> *Id.*

<sup>162</sup> *Id.*

<sup>163</sup> *Id.* at 486.

<sup>164</sup> *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*, 495 F.3d 695 (D.C. Cir. 2007).

<sup>165</sup> *Id.* at 697 (quoting *Moore v. East Cleveland*, 431 U.S. 494, 502 (1977)).

<sup>166</sup> *Id.* at 703.

<sup>167</sup> *Id.*

for drug regulation.<sup>168</sup> While the court conceded that a lack of governmental interference throughout history may be some evidence that a right is deeply rooted, the court noted that this lack of regulation was insufficient on its own.<sup>169</sup>

Furthermore, the court rejected Alliance's reliance on the three common law doctrines of self-preservation.<sup>170</sup> The court noted that Alliance offered little detail about how the common law doctrine of necessity applied to its case.<sup>171</sup> Rather, the court acknowledged that the Supreme Court's analysis of this doctrine in *Oakland Cannabis Buyer's Co-op*<sup>172</sup> left almost no leeway for the doctrine of necessity to override the FDCA.<sup>173</sup> In *Oakland Cannabis Buyer's Co-op*, the Supreme Court rejected an argument that medical necessity could be read into a statute which explicitly denied access to drugs, holding that the defense of necessity is invalid if Congress has statutorily limited its application.<sup>174</sup> In *Abigail Alliance*, Congress, through the FDCA, limited access to experimental drugs; consequently, the common law doctrine of necessity could not override the legislature's value judgment.<sup>175</sup> Additionally, the court abandoned the argument based on the tort of intentional interference with life-saving efforts, stating that such an action requires that aid be given to a person that is necessary to secure that person's bodily integrity.<sup>176</sup> There is no application of this principle to Alliance's case because the drugs have not been proven to be safe or effective so as to be necessary to save one's life.<sup>177</sup> Lastly, the court rejected Alliance's self-defense argument by refusing to accept that this case was about using reasonable force to defend oneself or about receiving access to medical treatment.<sup>178</sup> The court's decision turned on the fact that Alliance's patients could not "defend" themselves from harm by taking life-saving drugs with only the

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<sup>168</sup> *Id.* at 704•05.

<sup>169</sup> *Id.* at 706.

<sup>170</sup> *Abigail Alliance*, 495 F.3d at 707–10.

<sup>171</sup> *Id.* at 707–08.

<sup>172</sup> *United States v. Oakland Cannabis Buyer's Co-op*, 532 U.S. 483 (2001) (discussing the legality of providing marijuana to patients in violation of the Controlled Substance Act).

<sup>173</sup> *Abigail Alliance*, 495 F.3d at 708 (noting that in *Oakland* the Supreme Court held that Congress may limit or even eliminate a necessity defense that would under normal circumstances be available).

<sup>174</sup> *Id.*

<sup>175</sup> *Id.*

<sup>176</sup> *Id.*

<sup>177</sup> *Id.* at 710.

<sup>178</sup> *Id.*

*potential* for therapeutic effect.<sup>179</sup> The court found that Alliance was not arguing for the right of patients to defend themselves against a disease or harm, but only for the right to assume an enormous risk.<sup>180</sup>

The court found no fundamental right to access experimental drugs; hence, it applied a rational basis review to the government's regulations.<sup>181</sup> It was evident to the court that the government had a rational basis for guaranteeing "a scientifically and medically acceptable level of knowledge about the risks and benefits of such a drug; the FDA's policy of limiting access to investigational drugs is rationally related to the legitimate state interest of protecting patients, including the terminally ill, from potentially unsafe drugs with unknown therapeutic effects."<sup>182</sup>

While the August 2007 decision of the court of appeals was a roadblock for Alliance's effort, the group subsequently filed a petition for a writ of certiorari at the Supreme Court.<sup>183</sup> Even though certiorari was denied in early 2008, Alliance remains firmly committed to its cause, decreeing that the organization will continue to pursue the right to access investigational drugs in other federal circuit courts of appeal and, if necessary, in Congress.<sup>184</sup>

#### IV. AN EXERCISE IN FUTILITY: PHARMACEUTICAL COMPANIES LACK INCENTIVES TO VOLUNTARILY PROVIDE ACCESS TO INVESTIGATIONAL DRUGS.

Even with a favorable verdict, Alliance will not be successful in accomplishing access to post-Phase I experimental drugs through litigation. Pharmaceutical companies are private corporations, not state actors.<sup>185</sup> So, while the Constitution may require the removal of

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<sup>179</sup> *Abigail Alliance*, 495 F.3d at 710.

<sup>180</sup> *Id.* at 710.

<sup>181</sup> *Id.* at 713.

<sup>182</sup> *Id.*

<sup>183</sup> *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*, 495 F.3d 695 (D.C. Cir. 2007) (en banc), *petition for cert. filed*, 76 U.S.L.W. 3373 (U.S. Sept. 28, 2008) (No. 07-444).

<sup>184</sup> Press Release, *Abigail Alliance for Better Access to Developmental Drugs, Abigail Alliance Will Appeal D.C. Circuit Court Decision* (Aug. 22, 2007) (on file with author).

<sup>185</sup> A state actor is a person or entity acting on behalf of the government and is therefore subject to the U.S. Bill of Rights. *Lugar v. Edmonson Oil Co.*, 457 U.S. 922, 929-30 (1982). The Constitution does not grant affirmative rights but only protects individuals from the government infringing on constitutional rights not private individuals. *Deshaney v. Winnebago County Dep't of Soc. Serv.*, 489 U.S. 189, 195 (1989). Private individual entities have been converted to state actors when there is a close nexus between the government and the private sector, when the government

a government-imposed barrier such as a federal regulation to drug access, such a decision does not compel a private pharmaceutical company to grant such access, absent some statute. Thus, success in removing the legal barrier is only the first, albeit necessary step, and will not conclude the fight—Alliance will then have to convince drug companies to actually release the drugs or obtain passage of legislation commanding access. Such an outcome is unlikely. When the cost, practical infeasibilities, potential tort claim liability, ethical hurdles, and lack of infrastructure for such a program are considered, pharmaceutical companies are unlikely to provide experimental drugs unless drastic changes and accommodations are provided to protect them.

A. *Access to Experimental Drugs Is Practically Infeasible*

Assuming arguendo that drug manufacturers could voluntarily provide access to experimental drugs, they currently lack incentive to do so. The dynamics of the drug approval and development process make providing drugs early in the testing state practically infeasible. The main factors that control the incentives for providing access to these drugs are the fear of tort litigation, threat to clinical trials, limits to manufacturing capacity, possibility of harmful—or even deadly—effects of the drugs, and the lack of financial benefit.

1. Fear of Increased Tort Litigation

Every drug manufacturer has an ever-present concern for the possibility of tort litigation even after a new drug has been approved and has been on the market.<sup>186</sup> With unapproved, experimental drugs, the uncertainty of the drug's safety and effectiveness along with the possibility of unknown side effects creates a legitimate fear for manufacturers. Informed consent claims are the routine type of litigation that occurs with regard to unapproved drugs.<sup>187</sup> However, even these claims can be coupled with additional allegations under theories of strict product liability, failure to warn, negligence, and

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coerces, controls or encourages a private actor, when the action the private actor performs is traditionally a government function, or when the government and private actor participate in joint activity. See generally *Lugar*, 457 U.S. 922; *Rendell-Baker v. Kohn*, 457 U.S. 830 (1982); *Burton v. Wilmington Parking Auth.*, 365 U.S. 715 (1961); *Shelley v. Kraemer*, 334 U.S. 1 (1948).

<sup>186</sup> See Barnaby J. Feder, *Federal Panel Consolidates Vioxx Suits*, N.Y. TIMES, Feb. 17, 2005, at C1, for an example of volume and cost of tort litigation when issues of safety and effectiveness arise with an approved medication such as Vioxx.

<sup>187</sup> Michelle M. Mello et al., *The Rise of Litigation in Human Subjects Research*, 139 ANNALS OF INTERNAL MED. 40, 41 (2003).

fraud.<sup>188</sup> The implications of such litigation are obvious and severe: the cost of research and development will drastically increase and drug companies will have a disincentive to produce new cancer drugs.<sup>189</sup>

a. Informed Consent

Informed consent represents a crucial safeguard protecting human subjects participating in clinical trials for unapproved drugs.<sup>190</sup> All clinical trial investigators are required to obtain the consent of participants after providing a sufficient opportunity for consideration.<sup>191</sup> Information provided to the participant is required to be in clear, comprehensible language, and consent must contain both “a description of any reasonably foreseeable risks or discomforts” and a description of benefits to the subject which may reasonably be expected.<sup>192</sup> Additionally, investigators must provide a statement of the purpose and expectation of the study and a description of the trial procedures; for instance, whether the trial is a blind, randomized trial.<sup>193</sup> These particular facts are crucial to participants’ understanding that the study is not medical treatment but an experimental study. No informed consent may include any exculpatory language which waives or appears to release the sponsor from any liability for negligence.<sup>194</sup> Ultimately, informed consent seeks to ensure that each subject is competent to understand the information provided and willing to accept participation in investigational studies voluntarily without any undue influences.<sup>195</sup>

While its aim is to protect subjects in clinical trials, informed consent fails to be effective when a subject’s understanding of his access to the experimental drug is tainted by therapeutic misconception.<sup>196</sup> Therapeutic misconception occurs when a subject regardless of the information provided concerning the study nonetheless be-

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<sup>188</sup> *Id.*

<sup>189</sup> *Id.* at 44.

<sup>190</sup> See 21 C.F.R. § 50 (2007).

<sup>191</sup> *Id.* § 50.20.

<sup>192</sup> *Id.* § 50.20, 50.25(a).

<sup>193</sup> *Id.* § 50.25(a).

<sup>194</sup> *Id.* § 50.20.

<sup>195</sup> Sarah Hewlett, *Consent to Clinical Research—Adequately Voluntary or Substantially Influenced?*, 22 J. MED. ETHICS 232, 232 (1996).

<sup>196</sup> Paul S. Applebaum et al., *False Hopes and Best Data: Consent to Research and the Therapeutic Misconception*, 17 HASTINGS CTR. REPORT. 20, 20 (1987).



believes that the research project will benefit him directly.<sup>197</sup> A key factor in informed consent for subjects is the understanding that consent to use experimental drugs in a clinical setting is not the same as treatment.<sup>198</sup> Subjects under this misapprehension deny the possibility that there could be any disadvantages to participating in a study on experimental drugs.<sup>199</sup> Research shows that as many as seventy percent of subjects in clinical trials suffer from therapeutic misconception, believing that their participation is medical treatment for their personal needs.<sup>200</sup> Such a high percentage among subjects is substantiated when participants are questioned regarding their motivation for entering clinical trials. Instead of indicating a desire to assist in research for the good of cancer patients as a whole, most subjects indicate their participation in a trial was based on a desire to get advanced medical treatment, the hope of possibly benefiting in the absence of alternatives, and blind trust in their doctors' recommendation.<sup>201</sup> With this mindset, subjects do not pay particular heed to the information provided through the informed consent process.<sup>202</sup> In fact, many participants decide to participate in a clinical trial before even learning about the design of the study or signing the form.<sup>203</sup>

This misalignment of investigators' goals and participants' expectations regarding involvement in clinical trials creates a ripe setting for litigation. A current example of an informed consent claim derived from therapeutic misconception is the lawsuit sparked by the death of Jesse Gelsinger.<sup>204</sup> In September 1999, eighteen-year-old Jesse Gelsinger died from a reaction to a Phase I gene therapy treatment at the University of Pennsylvania's Institute of Human Gene Therapy.<sup>205</sup> Gelsinger suffered from a rare genetic illness which seriously affected his liver.<sup>206</sup> While his illness had left him hospitalized

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<sup>197</sup> Paul S. Applebaum, *Clarifying the Ethics of Clinical Research: A Path toward Avoiding the Therapeutic Misconception*, 2 AM. J. BIOETHICS 22, 22-23 (2002).

<sup>198</sup> Gail E. Henderson et al., *Clinical Trials and Medical Care: Defining the Therapeutic Misconception*, 4 PLOSMED. 1735, 1735 (2007), available at <http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0040324>.

<sup>199</sup> Applebaum, *supra* note 197, at 22.

<sup>200</sup> *Id.* at 23.

<sup>201</sup> Kass et al., *supra* note 70, at 25-26.

<sup>202</sup> *Id.*

<sup>203</sup> *Id.*

<sup>204</sup> Mello et al., *supra* note 187, at 41.

<sup>205</sup> Larry Thompson, *Human Gene Therapy: Harsh Lessons, High Hopes*, FDA CONSUMER, Sept.-Oct. 2000, available at [http://www.fda.gov/fdac/features/2000/500\\_gene.html](http://www.fda.gov/fdac/features/2000/500_gene.html).

<sup>206</sup> *Id.*

and seriously ill for many years, Gelsinger had been able to control his disease with diet and pills and lived as a normal, active teenager.<sup>207</sup> Although Gelsinger was considered healthy, Gelsinger's father encouraged him to participate in a Phase I study hoping there would be therapeutic benefit from the new therapy.<sup>208</sup> Four days after receiving the experimental treatment, Gelsinger died, but not from his disease—the experimental therapy caused multiple system failure.<sup>209</sup> Despite signing the informed consent form, the Gelsinger family, after Jesse's death, pursued an action with claims of informed consent, product liability, and fraud.<sup>210</sup> The Gelsingers claimed that the investigators failed to reveal information regarding the risks of the trial and that the principal investigator had a financial conflict of interest with the sponsor.<sup>211</sup> In the end, both parties reached a confidential settlement agreement in November 2000.<sup>212</sup>

The Gelsingers' lawsuit illustrates the possible issues created with informed consent and therapeutic misconception. Participants who refuse to understand the fundamental risk of experimental studies are left disappointed, angry, and confused when the trials do not produce an expected health benefit. This expectation, although unrealistic, has the potential to expose drug sponsors to increased tort litigation regardless of informed consent.

b. Application of Informed Consent to Alliance

The threat of informed consent litigation discourages pharmaceutical companies from allowing open access to experimental drugs. Even though Alliance's patients would not be clinical trial subjects, these patients would still be required to give informed consent for use of experimental drugs. Considering the novelty of providing investigational drugs outside of the clinical trial context, the dynamics of informed consent in clinical trials provides the best guide to assess how informed consent may or may not work in countering tort litiga-

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<sup>207</sup> *Id.*

<sup>208</sup> Sheryl Gay Stolberg, *Teenager's Death Is Shaking Up Field of Human Gene-Therapy Experiments*, N.Y. TIMES, Jan. 27, 2000, at A20.

<sup>209</sup> Thompson, *supra* note 205.

<sup>210</sup> Mello et al., *supra* note 187, at 41. It is important to note that the Gelsinger family's addition of a fraud claim exposed the pharmaceutical company to the possibility of increased damage awards. *Id.* Punitive damages occur in less than 1.5% of medical malpractice verdicts and approximately five percent of plaintiff trial wins overall. *Id.* at 42. However, punitive damage awards are exceptionally common among fraud claims, occurring in about one-fourth of verdicts for plaintiff. *Id.*

<sup>211</sup> *Id.*

<sup>212</sup> *Id.*

tion and setting proper expectations for Alliance's members. Clinical trial participants are a logical corollary to Alliance's members because the patients are voluntary and there will necessarily be limited knowledge about the drugs. Hence, one issue that arises is whether post-Phase I informed consent can ever even be given. With limited knowledge about the side-effects and possibly no information about effectiveness, the quantity and quality of information provided might not afford realistic or adequate expectations for the patient to make a proper decision to use the experimental drugs.

Therapeutic misconception may eliminate a patient's ability to make a knowing and voluntary decision to use investigational drugs even if there is informed consent. Similar to clinical trials, subjects receiving access to experimental medications are not receiving treatment. While they will not be exposed to the implications of blind, randomized studies, patients will still be receiving drugs which have not been proven effective, whose dosage has not been perfected, and whose side-effects are unknown. In a sense, while not officially participating in a trial, the patients are still "test rats" for the investigational drug. Studies of clinical trials have shown that patients who suffer from terminal illness are more likely to view taking experimental drugs as treatment and less likely to weigh all risks, benefits, and alternatives.<sup>213</sup> Since Alliance represents terminally ill patients who have exhausted their options, therapeutic misconception would most likely be a factor affecting the validity of its patients' informed consent and could lead to a "Gelsinger" situation where patients bring litigation when their expectation of the "treatment" is not satisfied or something tragic happens.

The possibility of informed consent claims surrounding access to experimental drugs provides a disincentive for pharmaceutical companies to allow access to unproven drugs. Pharmaceutical companies will be afforded very little protection from informed consent forms and will be left vulnerable to liability. Regardless of the validity of possible litigation, defending any actions translates into money lost. This increased cost to research and development could deter drug companies either from providing access or, even worse, from pursuing cancer drugs at all.

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<sup>213</sup> Monica H. Schaeffer et al., *The Impact of Disease Severity on the Informed Consent Process in Clinical Research*, 100 AM. J. MED. 261, 267 (1996).

## 2. Access to Experimental Drugs Could Hinder New Drug Development

Phase I access to experimental drugs creates a major concern for its effects on new drug development as a whole. The general fear is that accessing experimental drugs will have an impact and influence on the success of clinical trials. Clinical trials—the essential backbone of getting safe and effective new drugs to market—could be jeopardized with widened access as studies struggle for human subject recruitment. Currently, there is already a shortage of available and qualified subjects who may and are willing to participate in trials: only three percent of cancer patients in the United States are enrolled in clinical trials.<sup>214</sup> As discussed, a motivating factor in participation for these trials is the ability to access the drugs before they become available to the general public.<sup>215</sup> If available, patients will most likely choose access to drugs outside of the clinical study in order to avoid the possibility of receiving a placebo in a double-blind, randomized trial.<sup>216</sup> Additionally, if patients can access these drugs locally from their doctor, patients will have less incentive to travel to centers to participate in trials.<sup>217</sup> A shortage of patients willing to participate in studies could further extend the time and resources needed to complete pre-market studies.<sup>218</sup> Many cancer organizations, such as the National Coalition for Cancer Survivorship<sup>219</sup> and the National Breast Cancer Coalition,<sup>220</sup> have been unwilling to support Alliance's efforts,

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<sup>214</sup> Groopman, *supra* note 98, at 47.

<sup>215</sup> Kass et al., *supra* note 70, at 25–26.

<sup>216</sup> Kerry Howley, *Dying for Lifesaving Drugs: Will Desperate Patients Destroy the Pharmaceutical System That Produces Tomorrow's Treatments?*, REASON, Aug. 1, 2007, at 25, available at <http://www.reason.com/news/show/120763.html>.

<sup>217</sup> *Id.*

<sup>218</sup> Okie, *supra* note 55, at 437.

<sup>219</sup> The National Coalition for Cancer Survivorship (NCCS) is the oldest survivor-led cancer advocacy organization in the country, founded in 1986. NCCS, About NCCS, <http://www.canceradvocacy.org/about> (last visited Sept. 2, 2008). NCCS advocates for cancer care and cancer survivors, making its main priority patient education. *Id.* “NCCS believes in evidence-based advocacy for systemic changes at the federal level in how the nation researches, regulates, finances and delivers quality cancer care.” *Id.*

<sup>220</sup> The National Breast Cancer Coalition (NBCC) is a nationwide advocacy network consisting of 600 member organizations and 70,000 individual breast cancer activists. National Breast Cancer Coalition, NBCC History, [http://www.natlbcc.org/index.php?option=com\\_content&task=view&id=45](http://www.natlbcc.org/index.php?option=com_content&task=view&id=45) (last visited Sept. 2, 2008). Founded in 1991, the NBCC's goal is to eradicate breast cancer through promoting research and improving access to quality treatment and care. *Id.* Considered one of the most influential groups in health policy, NBCC continues to advocate for change in public policy, science, and industry “by creating new partnerships, collaborations, research funding opportunities and avenues for access to quality care.” *Id.*

fearing widening access will undermine these critical clinical studies and interfere with the progression of cancer research.<sup>221</sup>

Hesitation on the part of pharmaceutical companies to volunteer access to new drugs may also be valid; there is the possibility that complications or issues which arise with terminally ill users could later be used against the drug companies in evaluating or halting the approval by the FDA.<sup>222</sup> Physicians will bear the burden of prescribing these experimental drugs and attempting to administer the proper dosage and program based on the limited knowledge of risks, contraindications, and benefits.<sup>223</sup> Since these experimental drugs would not be administered in a controlled or regulated environment, any outcomes, either beneficial or tragic, could be misleading.<sup>224</sup> Apprehension arises when patients with different cancers start taking experimental drugs outside of the clinic trial context; researchers will be unable to determine which drugs work for which cancers and be unable to account for any outcomes—whether positive or negative.<sup>225</sup> Public sentiment to adverse reactions of drugs outside the clinical environment could unfairly interfere with the results of a clinical trial, possibly forcing the FDA to get involved in the investigation before submission of a NDA.

Overall, any possibility of prolonging or interfering with the drug approval process strongly eliminates incentives for pharmaceutical companies to continue with research and development of new drugs. Taking into consideration the rate of approval, costs, and the degree of risk, the market for cancer drugs is not as lucrative as it appears.<sup>226</sup> With only a few real blockbuster drugs for cancer treatment, drug companies, when faced with a business decision between devel-

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<sup>221</sup> See Press Release, National Coalition for Cancer Survivorship, Physician and Patient Care Groups Join (Feb. 6, 2007), available at <http://www.canceradvocacy.org/news/press/2007/physician-and-patient-care.html>; National Breast Cancer Coalition, Alliance's Petition to the FDA, [http://www.stopbreastcancer.org/index.php?option=com\\_content&task=view&id=76&Itemid=180](http://www.stopbreastcancer.org/index.php?option=com_content&task=view&id=76&Itemid=180) (last visited Sept. 8, 2008).

<sup>222</sup> Howley, *supra* note 216, at 6.

<sup>223</sup> Peter D. Jacobson & Wendy E. Parmet, *A New Era of Unapproved Drugs: The Case of Abigail Alliance v. Von Eschenbach*, 297 JAMA 205, 207 (2007).

<sup>224</sup> *Compassionate Use of Investigational New Drugs: Is the Current Process Effective?: Hearing Before the H. Comm. on Gov't Reform*, 107th Cong. 102 (2001) (Statement by Dr. Robert J. Temple, Associate Director of Medical Policy at the Center for Drug Evaluation and Research) [hereinafter *Compassionate Use Hearing*] (stating that industry concerns raised at the Oncology Drugs Advisory Committee meeting for access to experimental drugs were that the "use of an investigational drug in less controlled setting, in patients with very advanced disease could lead to adverse reactions that might raise difficult to resolve but spurious safety concerns about the drug").

<sup>225</sup> Groopman, *supra* note 98, at 46–47.

<sup>226</sup> *Id.*

oping a high-risk cancer drug or a new drug for cholesterol, for example, may choose to take a conservative approach and accept a fair rate of return by developing the cholesterol drug.<sup>227</sup> This dilemma will only be further aggravated if access to experimental drugs interferes with the clinical trials or it becomes difficult to identify which drugs are effective. There is considerable risk for cancer patients that there will be a “shift [in] investment from oncology to other areas where the development process is well defined and much less risky.”<sup>228</sup> If the cancer drug approval process becomes too laborious, companies may abandon cancer research all together.

### 3. Lack of Financial Incentive

The cost of development and production of new drugs can be astronomical for pharmaceutical companies.<sup>229</sup> The market for these drugs in Phase I will consist strictly of a subset of all terminally ill cancer patients, which is estimated at about 565,650 patients a year.<sup>230</sup> The challenge for pharmaceutical companies is to adequately price these new drugs to a fairly limited market so that using the drug is feasible for the manufacturer and patient.<sup>231</sup> Most likely, Medicare, Medicaid, and private insurers will not pay for experimental post-Phase I drugs.<sup>232</sup> Health insurers are willing to pay for treatments that are proven safe, effective, and medically necessary, but deny intervention coverage for emerging therapies.<sup>233</sup>

Hence, Medicaid and private health insurance companies customarily include in their policies provisions providing for the denial of “experimental” treatment, a term that has varying definitions and interpretations.<sup>234</sup> The possible ambiguity in the term “experimental” has led to recent litigation between insurers and women suffering from breast cancer seeking coverage for the “investigational” autologous bone marrow transplant (ABMT)<sup>235</sup> treatment, which had only

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<sup>227</sup> *Id.*

<sup>228</sup> *Id.*

<sup>229</sup> See *supra* note 94 and accompanying text.

<sup>230</sup> See *supra* note 2 and accompanying text.

<sup>231</sup> Groopman, *supra* note 98, at 46–47.

<sup>232</sup> Okie, *supra* note 55, at 440.

<sup>233</sup> John Cova, *A Swift Response to a “Modest” Proposal*, 84 J. NAT’L CANCER INST. 744, 744 (1992) (noting that insurers are not responsible for funding clinical research).

<sup>234</sup> Angela Holder, *Funding Innovative Medical Treatment*, 57 ALB. L. REV. 795, 795–96 (1994).

<sup>235</sup> ABMT is an aggressive procedure to treat Stage IV cancer by which bone marrow is extracted from the patient and frozen while the patient undergoes unusually high doses of chemotherapy. *Pirozzi v. Blue Cross-Blue Shield of Va.*, 741 F. Supp. 586, 588 (E.D. Va. 1990). When the chemotherapy is complete, the bone marrow is

been through Phase II testing.<sup>236</sup> Applying contract law, many courts have construed the ambiguity of policy language against the insurer and many women were successful in receiving coverage for this intervention because courts deemed it to be potentially life-saving medical treatment.<sup>237</sup> Nonetheless, many courts have sided with the insurance company's denial of ABMT treatment because the intervention qualified as experimental and the policy language was clear.<sup>238</sup> Most likely, as a result of this litigation, insurance companies will have removed all ambiguities in coverage in regards to "experimental" drugs. Even if such ambiguity still exists, courts will potentially be less likely to side in favor of a patient when the drug has only been through Phase I trials in contrast to ABMT which had completed Phase II. Additionally, the subsequent FDA denial of Phase III approval of the ABMT procedure<sup>239</sup> established a strong warning for the courts that drugs which have not properly finished testing are still experimental and can fail for lack of efficacy. Considering this progression, it is likely that the terminally ill will be forced to pay out of pocket for the expenses of these investigational drugs.

In addition to a lack of insurance coverage to compensate for drug use, if the pharmaceutical companies find it necessary to track and monitor these experimental drugs, the additional costs—above research and development and clinical trials—might be too high to make providing access worthwhile.<sup>240</sup> In its complaint, Alliance argued that the experimental drugs should be able to be sold at a profit by the pharmaceutical companies in order to encourage participa-

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restored in the patient. *Id.* This treatment requires at least a ten-day hospital stay and follow-up medical care costing on average \$100,000. *Id.* At the time of the litigation, ABMT had not been tested in a Phase III study. *Id.*

<sup>236</sup> See *infra* notes 237–38.

<sup>237</sup> See, e.g., *Adams v. Blue Cross/Blue Shield of Md., Inc.*, 757 F. Supp. 661, 663 (D. Md. 1991); *Bucci v. Blue Cross-Blue Shield of Conn.*, 764 F. Supp. 728, 731 (D. Conn. 1991); *Pirozzi*, 741 F. Supp. at 595; *Taylor v. Blue Cross/Blue Shield of Mich.*, 517 N.W.2d 864, 867–69 (Mich. Ct. App. 1994); *Waldrup v. Conn. Nat'l Life Ins. Co.*, 566 So. 2d 434, 437 (La. App. 1990).

<sup>238</sup> See, e.g., *Harris v. Mutual of Omaha Cos.*, 992 F.2d 706, 712–13 (7th Cir. 1993); *Holder v. Prudential Ins. Co. of Am.*, 951 F.2d 89, 90–92 (5th Cir. 1992); *Hasty v. Cent. States, Se. & Sw. Areas Health & Welfare Fund*, 851 F. Supp. 1250, 1255–60 (N.D. Ind. 1994).

<sup>239</sup> For a discussion on why ABMT subsequently failed to prove effective in randomized clinical trials after over 30,000 women had unnecessarily received this drastic treatment, see *The Breast Cancer HDCT/Transplant Debacle: Why Did It Happen, and Could It Happen Again*, 16 ONCOLOGY NEWS INT'L, Sept. 2007, available at <http://www.cancernetwork.com/showArticle.jhtml?articleId=201805399>.

<sup>240</sup> Okie, *supra* note 55, at 440.

tion.<sup>241</sup> This change would be in direct opposition to the FDA's current regulations regarding "compassionate-use" exceptions that strictly prohibit the companies from making a profit on investigational drugs.<sup>242</sup> This departure from the current standard embodies Alliance's belief, and the libertarian perspective, that the terminally ill have the right to autonomy, to make personal self-dealing choices about their lives and their medical treatment—including whether to pay out-of-pocket for access to investigational drugs.<sup>243</sup> While Alliance advocates for patients' autonomy to make decisions to pay for investigational drugs, the FDA's resistance focuses on the patient's potential vulnerability—willingness to sacrifice their savings and over-extend their credit for pricey medications which offer no value and possibly just false hope.<sup>244</sup> However, Alliance argues for the possibility of this hope, regardless of its legitimacy, at any cost to the patient.<sup>245</sup> Considering a best-case scenario under Alliance's plan, the drug companies would need to find a balance in price between covering their costs (not necessarily making a profit) and making the drug affordable to the patient. However, maintaining this balance poses a challenge for approved, marketable drugs, making it unlikely drug companies will find a price that provides them with an incentive to offer access to experimental drugs outside of clinical studies, while making the drug affordable to patients of varying incomes.

#### 4. Limits to Manufacturing Capacity

Production of new drugs is indirectly dictated by and tailored to the FDA's regulations on drug approval.<sup>246</sup> This FDA-centrism<sup>247</sup> controls the amount of drugs produced. Considering the size of clinical trials, ranging from a few hundred subjects to a few thousand, batches prepared for these studies are particularly small.<sup>248</sup> Hence,

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<sup>241</sup> *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*, 495 F.3d 695, 700 (D.C. Cir. 2007) (en banc).

<sup>242</sup> 21 C.F.R. 312.7(d)(3) (2008).

<sup>243</sup> Brief of Appellant's Resp. to Appellee's Pet. for Panel Reh'g and Reh'g *En Banc* at 6–7, *Abigail Alliance*, 495 F.3d at 700.

<sup>244</sup> See George J. Annas, *Faith(Healing), Hope, and Charity at the FDA: The Politics of AIDS Drug Trials*, 34 VILL. L. REV. 771 (1989), for a discussion that expanding access to investigational AIDS medications is bad public policy because it exploits vulnerable patients who are looking for hope at any cost.

<sup>245</sup> See *infra* text accompanying note 259.

<sup>246</sup> Jeffrey N. Gibbs, *State Regulation of Pharmaceutical Clinical Trials*, 59 FOOD & DRUG L.J. 265, 265 (2004).

<sup>247</sup> *Id.*

<sup>248</sup> Tom Class, *Expanded Access to Unapproved Medical Products: Compassionate Use*, REG. AFF. FOCUS, May 2006.



allowing access to experimental drugs would require a major investment in resources to increase production for this new market.<sup>249</sup> For example, ImClone has cited, as its critical roadblock in providing to compassionate-use programs the drug Erbitux (the drug Abigail Burroughs was denied), its constraints and limits in the manufacturing process for these specialized drugs.<sup>250</sup> Due to limited manufacturing capacity and lack of out-sourcing facilities, ImClone was forced to prioritize drug production and allocate all drugs to clinical trials, eventually terminating its participation in any expanded use program.<sup>251</sup> In order to meet even this limited demand of the clinical trials and the expanded use programs, ImClone built its own facility to ensure an adequate supply of the drugs, accepting the risk that Erbitux might never be approved.<sup>252</sup>

Drug companies would be reckless to consider increasing production of drugs at any cost when the drugs do not qualify as medical treatment and have the potential to exacerbate a patient's condition or even cause death. It is not reasonable to invest in the resources to increase manufacturing when there is no evidence that the drug is effective and ultimately will be financially viable.<sup>253</sup> Yet another factor to consider is that in the early phases of the approval process drug companies are still figuring out how to best manufacture the product.<sup>254</sup> By rushing this process, the manufacturing of these drugs—which still only have a six percent chance of FDA approval<sup>255</sup>—might not be optimal both for the patient's health and for cost efficiencies in production for the company.

##### 5. Access to Experimental Drugs Could Raise Ethical Issues for Pharmaceutical Companies

Providing access to experimental drugs pushes the boundaries on ethical issues for both the FDA and pharmaceutical companies. Due to the nature and gravity of their business, pharmaceutical com-

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<sup>249</sup> Groopman, *supra* note 98, at 45; *see also* *Compassionate Use Hearing*, *supra* note 224 (statement by Dr. Robert J. Temple, Associate Director for Medical Policy at the Center for Drug Evaluation and Research) (citing limits to drug supply and the cost of increasing such a supply as an industry concern in providing access to investigational drugs).

<sup>250</sup> *Compassionate Use Hearing*, *supra* note 224, at 113–14 (statement by Dr. Samuel Waksal, President and CEO of ImClone Systems, Inc.).

<sup>251</sup> *Id.*

<sup>252</sup> *Id.* at 120.

<sup>253</sup> Class, *supra* note 248, at 13.

<sup>254</sup> Okie, *supra* note 55, at 440.

<sup>255</sup> *See id.* at 439.

panies have an ethical obligation to provide the highest quality products. Since the 1962 Amendments to the FDCA, the FDA has accepted the obligation to responsibly regulate drugs and strengthen its identity as a consumer protection agency.<sup>256</sup> These obligations can conflict with the increasing emphasis on individual autonomy in American society and law.<sup>257</sup> For instance, Alliance argues that the government is too paternalistic, in that terminally ill patients should be allowed to accept the greater risk in taking experimental drugs.<sup>258</sup> Alliance strongly believes that

these decisions depend greatly on the patient's values and individual life circumstances as well as his or her cold assessment of the statistical response rates. Are the last days of a person's life better spent in perhaps a painful struggle against nearly impossible odds, but with some hope and the conviction that he or she is doing everything possible? Or is it instead better or more noble to accept one's fate and spend the final days saying goodbye and hoping passively for a spontaneous remission? Is a 10% chance of living an extra month worth hazarding a risky and painful treatment that will degrade the patient's remaining life? Certainly [Alliance] does not know the right answers for every patient. Neither . . . does the FDA.<sup>259</sup>

Alliance claims that to deny a right to accept a heightened risk can be viewed as administering a death sentence to sick patients.<sup>260</sup> On the other hand, the FDA and drug companies have a duty to protect patients. Permitting companies to market drugs without evidence of efficacy could create "massive opportunity for fraud, involving people who are very sick and very desperate."<sup>261</sup> Since unapproved experimental drugs are not medical treatments, distribution of these drugs to those who are desperate and dying seems unethical and cruel. Arguments have been raised that allowing access to experimental drugs is bad public policy because it only offers false hopes to the sick, inducing patients to spend energy and money grasping at straws.<sup>262</sup>

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<sup>256</sup> Annas, *supra* note 244, at 772.

<sup>257</sup> JANET L. DOLGIN & LOIS L. SHEPHERD, *BIOETHICS AND THE LAW* 48 (2005).

<sup>258</sup> *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*, 495 F.3d 695, 699 (D.C. Cir. 2007).

<sup>259</sup> Brief of Appellant's Resp. to Appellee's Pet. for Panel Reh'g and Reh'g *En Banc* at 7, *Abigail Alliance*, 495 F.3d at 700.

<sup>260</sup> Sue Korach, *The Abigail Alliance: Motivated by Tragic Circumstances, Families Battle an Uncaring Bureaucracy*, *LIFE EXTENSION* 25 (2007), available at <http://abigail-alliance.org/LEMSEP07pAbigailLR.pdf>.

<sup>261</sup> Okie, *supra* note 55, at 437.

<sup>262</sup> Annas, *supra* note 244, at 785–87.

Both views on the ethics of supplying experimental drugs interpret compassion differently. For patients, compassion means allowing the right to choose to accept a greater risk at the slight chance a benefit might be received; for drug companies and the FDA, compassion is not supplying ill patients with promises and hope until a drug can be proved safe and effective.<sup>263</sup> While there may be no right or wrong answer, such considerations will come into play as drug manufacturers decide whether to voluntarily provide experimental drugs outside of clinical trials, upsetting the current balance between protecting the safety of individuals and respecting the decision of those who are dying.

#### V. AN ALTERNATIVE APPROACH: A LEGISLATIVE SOLUTION

While Alliance has attempted, albeit unsuccessfully, to achieve its goals through the judicial system, legislators are seeking to expand access to experimental drugs for Alliance's terminally ill members through proposed amendments to the FDCA. On November 3, 2005, Senator Sam Brownback (R-KS) introduced the Access, Compassion, Care and Ethics for Seriously-Ill Patients Act (ACCESS) which details a transformation in the current FDA drug approval system for terminally ill patients, specifically an expansion on approval of fast-track products.<sup>264</sup> ACCESS shifts the decision for terminally ill patients to take investigational drugs to patients and their physicians, and consequently away from the government.<sup>265</sup>

##### A. ACCESS's Proposal for a Reformed Drug Access Program for the Terminally Ill

ACCESS proposes to amend the FDCA to expand access to investigational drugs for seriously ill patients who have exhausted all treatment options, maintaining that the current drug approval standards "deny the benefits of medical progress to seriously ill patients who face morbidity or death from their disease."<sup>266</sup> The Act identifies numerous roadblocks in the current structure that limit more expedited access to investigational drugs such as the necessity of placebo

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<sup>263</sup> See *id.* at 792 ("True autonomy requires adequate and accurate information upon which to base decisions. This is simply impossible in the absence of reasonable scientific study and properly designed clinical trials.").

<sup>264</sup> Access, Compassion, Care and Ethics for Seriously-Ill Patients Act, S. 1956, 109th Cong. (1st Sess. 2005); see 21 U.S.C. § 356 (2000).

<sup>265</sup> Access, Compassion, Care and Ethics for Seriously-Ill Patients Act, S. 1956, 109th Cong. (1st Sess. 2005).

<sup>266</sup> *Id.* § 2.

controlled studies, failure of compassionate-use programs, over-reliance on conservative statistical analysis of clinical information compared to a clinical evaluation, and the inability of sponsors to interact with the FDA in a prompt manner.<sup>267</sup> In response to these hurdles, the Act recommends an enhanced multi-tiered drug approval process for this specific target group of terminally ill patients.<sup>268</sup>

ACCESS seeks to allow companies to market drugs after Phase I and II—if approved and with appropriate warnings and controls—strictly to the seriously ill who have exhausted all available medical treatment.<sup>269</sup> The bill alleviates the strict requirements of clinical testing for market approval in Phase I and creates a new standard for evaluation of an application.<sup>270</sup> For a Phase I experimental drug to be approved for access, the application must show enough preliminary evidence of effectiveness for the FDA to determine “whether the totality of the information available . . . regarding the safety and effectiveness of an investigational drug . . . as compared to the risk of morbidity or death from a condition or disease, indicates that a patient . . . may obtain more benefit than risk if treated with the drug.”<sup>271</sup> When an application is approved, provided the benefits outweigh the risks, the bill requires that as a condition to receiving the product a patient must (1) provide written informed consent, (2) provide a written waiver of the right to sue the manufacturer, sponsor, physician, or institution for any adverse events caused by using the drugs, enforceable in both state and federal court, and (3) provide consent to allow the sponsor to obtain information on their usage for support of their drug application.<sup>272</sup>

Beyond creating more flexibility in the approval process for Phase I drugs and alleviating some drug companies’ concerns, the ACCESS Act requires the Secretary of Health and Human Services to establish an internal infrastructure to support such a program, and more importantly, to create additional regulations regarding clinical

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<sup>267</sup> *Id.* §§ 2–3.

<sup>268</sup> *Id.* §§ 2–3.

<sup>269</sup> *Id.*

<sup>270</sup> *Id.* (requiring a sponsor to submit an application which contains data and information “from completed Phase I clinical investigations and *any other non-clinical* or clinical investigations . . . [which show preliminary evidence of effectiveness] based on uncontrolled data such as case histories, information about the pharmacological mechanism of action, data from animal and computer models, comparison with historical data, or other preliminary information . . .”) (emphasis added).

<sup>271</sup> Access, Compassion, Care and Ethics for Seriously-Ill Patients Act, S. 1956, 109th Cong. § 3 (1st Sess. 2005).

<sup>272</sup> *Id.* § 3.

studies and evaluations.<sup>273</sup> For example, ACCESS mandates the formation of an Accelerated Approval Advisory Committee, consisting of independent, non-government professionals, to review applications and issue recommendations to the Secretary for the purpose of expediting the approval process.<sup>274</sup> Also, Senator Brownback proposes an Expanded Access Program that specifically focuses on developing a plan to recognize and predict drugs that are likely to have a clinical benefit for life-threatening conditions and to make available a public list of all drugs under investigation which may be candidates for Phase I and II marketing approval.<sup>275</sup>

Much more drastic than these two provisions, ACCESS also flatly prohibits placebo-only or non-treatment-only controls in clinical trials with “respect to any life-threatening condition or disease where reasonably effective approved alternative therapies exist for the specific indication.”<sup>276</sup> This regulation ensures patients would not be pressured into a controlled clinical environment, where they may or may not receive an experimental drug, provided that a reasonable drug has been approved for this specific use by the agency in the expanded use program. Finally, in evaluating clinical information, the Act instructs the Secretary to give equal weight to clinical judgment and statistical analysis<sup>277</sup> to determine safety and effectiveness, prohibiting denial of an application “based solely on the basis of a statistical analysis or the rigid use of the ninety-five percent confidence level convention.”<sup>278</sup>

*B. Response to ACCESS by Interest Groups*

Critics have labeled ACCESS as “bad law,” noting many of the similar criticisms and concerns identified in Alliance’s proposal and

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<sup>273</sup> *Id.* §§ 2–6.

<sup>274</sup> *Id.* § 3.

<sup>275</sup> *Id.*

<sup>276</sup> *Id.* § 4.

<sup>277</sup> Access, Compassion, Care and Ethics for Seriously-Ill Patients Act, S. 1956, 109th Cong. § 6 (1st Sess. 2005). The ACCESS Act notes that non-statistical measures shall include but are not limited to: clinical evaluation information such as case history reports, scientific and clinical studies designed to measure or define mechanisms of action or molecular targeting, data from animal and computer models, comparisons with historical data, evaluations of the adverse effect of delaying the availability of an investigational drug to even a small subpopulation of seriously ill patients and scientific, observational, or clinical studies designed and conducted to collect well-documented information. *Id.*

<sup>278</sup> *Id.* § 6.

litigation.<sup>279</sup> The clinical research community is most alarmed, questioning the lenient standard of approval for Phase I drugs and the sponsor's confidence in evidence of drug efficacy without randomized trials.<sup>280</sup> Specifically, there is concern that the Act's allowance of pre-clinical data to be evaluated by a risk-benefit standard may cause all drugs to appear promising.<sup>281</sup> The Society of Clinical Trials notes that sponsors only proceed with drug approval past Phase I if the drugs are promising, but the harsh reality is that most cancer drugs (indeed, most drugs treating any disease) eventually fail for efficacy or safety reasons.<sup>282</sup> The general fear is that the terminally ill will be faced with broad access to experimental drugs, but in actuality access will be gained only to ineffective and harmful drugs without any means to qualify these drugs for decision-making purposes.<sup>283</sup>

The clinical community has also challenged the bill's repudiation of the accepted scientific method for testing drugs.<sup>284</sup> While critics concede that the drug approval process is rigorous, history has shown that the most reliable data and information is obtained from randomized clinical trials.<sup>285</sup> Interference with this gold standard of testing has the potential to undermine years of medical and scientific findings.

Lastly, critics raise ethical issues regarding ACCESS directed at protecting terminally ill patients from coercion and liability assumption. By permitting marketing approval post-Phase I, drug companies will be permitted to charge for their experimental drugs.<sup>286</sup> Without any controls on pricing, companies may take advantage of vulnerable patients.<sup>287</sup> Such susceptibility increases when patients are required to assume all liability for risk.<sup>288</sup> While allowing a blanket waiver of liability is the price to be paid to motivate participation by the drug companies, patient advocates are concerned that ACCESS

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<sup>279</sup> Colin Begg et al., *The Society for Clinical Trials Opposes US Legislation to Permit Marketing of Unproven Medical Therapies for Seriously Ill Patients*, 3 CLINICAL TRIALS 154, 157 (2006).

<sup>280</sup> *Id.* at 155–56.

<sup>281</sup> *Id.* at 155.

<sup>282</sup> *Id.*

<sup>283</sup> *Id.*

<sup>284</sup> *Id.*

<sup>285</sup> Begg et al., *supra* note 279, at 155.

<sup>286</sup> *Id.*

<sup>287</sup> *Id.*

<sup>288</sup> George J. Annas, *Cancer and the Constitution—Choice at Life's End*, 357 NEW ENG. J. MED. 408, 411 (2007).

does not provide the appropriate balance for protection of patient rights and interests.<sup>289</sup>

On the other hand, the bill has attracted strong supporters and advocates for expanding patients' rights. Supporters have defended the more flexible Phase I approval standard for the terminally ill by claiming that time spent in pre-clinical testing does not necessarily prevent drug tragedies because doctors and drug companies tend to learn more about drugs after approval than before.<sup>290</sup> Those who defend ACCESS hold firm to the conviction that it is unethical to expose seriously ill patients to the potential use of placebo medications in a clinical trial.<sup>291</sup> Despite this support, currently the ACCESS Act has not been enacted.<sup>292</sup>

C. *FDA Responds with Proposed Expanded Access to Investigational Drugs for Treatment Use Rule*

The FDA has initiated its own proposal to expand access to investigational new drugs for patients with serious life-threatening diseases who lack therapeutic options.<sup>293</sup> This proposed rule—the Expanded Access to Investigational Drugs for Treatment Use (EAID)—augments the extant expanded access programs by clarifying and amending the existing regulations.<sup>294</sup> These regulations work at improving the effectiveness of the existing “compassionate-use” programs by addressing the inconsistencies in the application process, elaborating on the requirements and safeguards in the programs, and creating flexibility in the review process on a case-by-case basis.<sup>295</sup>

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<sup>289</sup> *Id.*

<sup>290</sup> Univ. of Texas Anderson Cancer Ctr., *Phase I Clinical Trials Program: Improving Access to Investigational Drugs*, 3 BENCH TO BEDSIDE & BACK, Winter / Spring 2007, at 1.

<sup>291</sup> *Id.*

<sup>292</sup> KaiserNetwork.org, Kaiser Daily Health Policy Report: Lawmakers to Reintroduce Bill Legalizing Terminally Ill Patients' Access to Experimental Medications (Aug. 17, 2007), [http://www.kaisernetwork.org/daily\\_reports/print\\_report.cfm?DR\\_ID=46955&dr\\_cat=3](http://www.kaisernetwork.org/daily_reports/print_report.cfm?DR_ID=46955&dr_cat=3) (last visited Nov. 4, 2008).

<sup>293</sup> Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. 75,147 (Dec. 14, 2006) (to be codified at 21 C.F.R. pt. 312).

<sup>294</sup> *Id.*

<sup>295</sup> *Id.* at 75,149–51.

The FDA clearly identifies the main goal of this rule to address concerns including inconsistent application of access policies and programs and inequities in access based on relative sophistication of the setting in which a patient is treated or on the patient's disease or condition. By describing in detail in the proposed rule the criteria, submission requirements, and safeguards for the different types of expanded access for treatment uses of investigational drugs, the agency seeks to increase awareness and knowledge of expanded use programs

The EAID rule mandates three criteria to qualify for the expanded use programs.<sup>296</sup> First, the patient must suffer from a serious disease or a condition lacking satisfactory therapeutic treatment alternatives.<sup>297</sup> While this is consistent with the current regulation, the FDA clarifies the “lack of comparable or satisfactory therapeutic alternatives” to mean that the patient has exhausted all available FDA-approved therapies and has failed to respond to these therapies or is intolerant of them.<sup>298</sup> In addition, the FDA may require the patient to exhaust treatment options not regulated by the FDA if such alternatives are supported by compelling literature evidence.<sup>299</sup> A second criterion for the proposed expanded use program is that the FDA “must determine that the potential patient benefit justifies the potential risks of the treatment use and that those potential risks are not unreasonable in the context of the disease or condition to be treated.”<sup>300</sup> The final criterion states that the FDA must assure that providing access to investigational drugs will not interfere with any stage of clinical testing.<sup>301</sup> With the concern of protecting clinical testing, the EAID rule restricts acceptance into the expanded use program for any individuals able to participate in a clinical trial, but recognizes that participation will not be denied if the patient has been rejected from a trial due to their stage of the disease, has an intolerance to the active control in the randomized trial, or has limitations due to geographical location that make participation in a trial impossible.<sup>302</sup>

While EAID focuses on elaborating on the current expanded use programs, the proposed rule makes a drastic concession to proponents of both Alliance’s mission and the ACCESS Act. The proposed regulation fails to require a particular level of safety or effectiveness to merit access to an investigational drug, leaving such decisions to be determined on an individualized basis by evaluating the seriousness

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and the procedures for obtaining investigational drugs. Increased knowledge and awareness about expanded access options should make investigational drugs more available in the appropriate situations.

*Id.* These goals address the weaknesses of “compassionate-use” programs identified before Congress. *See Compassionate Use Hearing, supra* note 224.

<sup>296</sup> Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. 75,150–51 (Dec. 14, 2006) (to be codified at 21 C.F.R. pt. 312).

<sup>297</sup> *Id.* at 75,150–51.

<sup>298</sup> *Id.*

<sup>299</sup> *Id.*

<sup>300</sup> *Id.*

<sup>301</sup> *Id.*

<sup>302</sup> Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. 75,147, 75,153 (Dec. 14, 2006) (to be codified at 21 C.F.R. pt. 312).



of the disease and the size of the group.<sup>303</sup> The proposal dictates that as the seriousness of a patient's disease increases, access to investigational drugs which have completed Phase I testing and have been supported by preliminary evidence of effectiveness could be increased.<sup>304</sup> However, as the patient-group size grows—for example, if the expanded use application is submitted on behalf of larger patient populations—the FDA will demand a higher level of evidentiary findings for safety and effectiveness.<sup>305</sup> Most likely, drugs will have to be tested through Phase II or III.<sup>306</sup> The EAID regulation creates a mechanism for the FDA to balance all the information available—testing results on safety and effectiveness, seriousness of the disease, and size of the sample group—to come to an individualized decision for each submission which responsibly assesses the benefits and risks.

While patients are given the possibility of increased flexibility for the opportunity of gaining access, EAID leaves the practical burden of meeting compliance standards for the program on physicians and drug companies.<sup>307</sup> To initiate the entire process, drug manufacturers or sponsors are obligated to file a detailed submission under the expanded access program to qualify its drug for access.<sup>308</sup> If approved, the drugs will be administered by a sponsoring physician or “investigator” who is required to report adverse experiences to the sponsor, ensure informed consent, obtain Institutional Review Board approval, and maintain case histories and drug disposition records.<sup>309</sup> Additionally, the proposal suggests that the FDA has the authority to require the sponsor to monitor a patient's use of an investigational drug, if access to this drug is authorized to continue past the rule's limited duration of a single course of therapy.<sup>310</sup>

#### VI. THE BEST PROMISE OF HOPE: FDA'S EXPANDED ACCESS TO INVESTIGATIONAL DRUGS FOR TREATMENT USE RULE

The success of a program permitting access to investigational drugs demands participation and cooperation among Congress, the FDA, pharmaceutical companies, physicians, and patients, coupled

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<sup>303</sup> *Id.* at 75,151.

<sup>304</sup> *Id.*

<sup>305</sup> *Id.*

<sup>306</sup> *Id.*

<sup>307</sup> *Id.* at 75,151–52.

<sup>308</sup> Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. 75,147, 75,152 (Dec. 14, 2006) (to be codified at 21 C.F.R. pt. 312).

<sup>309</sup> *Id.*

<sup>310</sup> *Id.* at 75,153.

with a compromise on the balance between patient autonomy and consumer protection. Unfortunately, Alliance's litigation, the ACCESS Act, and the proposed EAID rule all miss the mark in this respect. Alliance's litigation makes large demands on behalf of its members without implementation of any infrastructure to support the envisioned changes. On the other hand, the ACCESS Act provides the necessary structure through practical concessions for liability waivers, pricing provisions, and the establishment of committees and boards to implement the program. However, the ACCESS Act's overly lenient approval process and disregard for established clinical testing methods make it too controversial to muster the required support to get the bill approved. Although Congress is the proper forum to address this issue, the proposed EAID rule strikes the desired compromise between patient autonomy and consumer protection by expanding and clarifying the already existing "compassionate-use" programs. However, maintaining this new balance will still require more incentives to encourage drug company participation.

Ironically, and most likely a result of Alliance's lobbying, the FDA itself is seeking to shift the balance and to formulate a reasonable compromise, blending aspects of Alliance's and the ACCESS Act's goals with a more conservative consumer protection approach. The FDA is obviously in a precarious position because any change opens the agency up for criticism if insidious drug access is allowed. Conversely, if the agency does not act quickly enough, it will be criticized for being too restrictive in getting effective drugs to the market. Clearly neither perspective—the libertarian or the liberal—will ever be totally satisfied; however, if compromise is to be made between both perspectives (which is obviously debatable), the FDA has found the appropriate compromise by evaluating each expanded access use on a case-by-case basis. By improving on an already established program, the FDA's proposal allows the agency to maintain its role as consumer protectors but affords the flexibility—only when all circumstances align properly—for the FDA to meet the desire of dying patients to accept the potential risk of using experimental drugs.

However, even the FDA admits that its own proposal may be futile due to its lack of authority to compel drug companies to supply investigational drugs to patients.<sup>311</sup> Concerns about liability, therapeutic misconception, manufacturing capacity, informed consent,

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<sup>311</sup> *Id.* at 75,150 ("While this proposed rule aims to clarify, and thereby expand, the situations in which expanded access to unapproved drugs could be available, under its existing authority, FDA cannot compel a drug manufacturer to provide access to investigational drugs for treatment use.").

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and pricing are left largely unaddressed. To make this proposal effective, revisions must be made to encourage drug company participation and to further protect patients. First, the proposal must provide a safeguard for therapeutic misconception by creating an evaluation process whereby the patient is counseled and educated regarding the drug and instructed that no personal benefit may be gained from its use. This process should be headed by the FDA or Institutional Review Boards, incorporating either the sponsor or the physician, and the patient's comprehension and state of mind regarding their access should be a factor in determining access. While this may be an administrative and logistical burden, this procedural safeguard protects patients and should involve the implementation of a waiver of liability for sponsors, manufacturers, and physicians who encourage participation in the program. Patients who are demanding the right to assume the risk of experimental drugs must concede any claims of liability to make the program effective. This concession is balanced by a patient-protective informed consent process; a liability waiver will not be coercive or unethical provided a safeguard is in place to counteract therapeutic misconception by balancing the reality of the risk with the possible benefits.

The EAID proposal also needs to specifically address the pricing of experimental drugs through the expanded access program. The provisions of EAID place increased burdens on drug companies, in regard to their involvement in the expanded access program, yet fail to create any incentives for the drug companies to accept these encumbrances. The proposal only allows companies to be reimbursed for direct and select administrative costs. Experimental drugs should be priced so as to permit pharmaceutical companies to break even on their production of the drugs. This break-even price should include the administrative costs of running and monitoring an expanded use program, an allocation of production fixed and variable costs, cost of delivering investigational drugs, and an allocation of the research and development costs. Additionally, the drug sponsor should incorporate into the price a fixed percentage increase on the base costs accounting for the historical percentage of losses incurred in its expanded use program from production of drugs which are never utilized. This provision encourages manufacturers to increase production for the expanded use programs without the fear of being stuck with the financial costs and a stockpile of drugs if the drugs are never accepted in the program or if the drugs are subsequently found not to be safe and effective. Obviously, these favorable pricing concessions raise ethical and fairness issues for patients: either only the

wealthy will be able to afford the medications or desperate patients will be forced to sacrifice their life savings for the hope of some therapeutic benefit. As part of this comprehensive program, the government must consider practical ways to fund access for patients in need. One suggestion may be to create a common patient pool of funds contributed by drug companies, the government, private citizens, and interest groups.

Finally, the proposed EAID rule needs to address the manufacturing capacity lag identified as a problem by pharmaceutical companies in supplying drugs to the current compassionate-use program.<sup>312</sup> The major roadblock in the current compassionate-use program is the time constraints for drug companies to ramp up production of new investigational drugs.<sup>313</sup> In order to overcome these manufacturing-time limitations, the EAID must implement a committee and process whereby investigational drugs are identified as potential drugs for compassionate-use. This would involve increased communication between drug manufacturers and the FDA about the sponsor's progress in clinical trials and pre-emptive discussions with scientific and medical experts as to their recommendations. Early identification, coupled with a provision that allows companies to be reimbursed through the pricing mechanism for wasted production, will help encourage drug companies to start increasing manufacturing capacity as soon as reasonably possible.

## VII. CONCLUSION

The tension between the promotion of safe and effective drugs and the demand for faster approval is a natural and inevitable consequence of pre-market drug approval. Competing interests will continue to push and pull in opposing directions, while the government, fearing the backlash of a Thalidomide-like disaster, hopes to find a balance that satisfies and protects both patients and drug companies. A perfect balance, of course, may not be achievable, but the closest and easiest compromise comes in the FDA's form of individualized exceptions. The FDA's proposed EAID rule manages to address and attempt to fix the failures in the current compassionate-use program, while also expanding the program to allow the possibility of meeting Alliance's demands for post-Phase I access to experimental drugs.

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<sup>312</sup> See *Compassionate Use Hearing*, *supra* note 224, at 113–15 (statements from Dr. Waskal of ImClone) (stating that manufacturing has been the major roadblock for getting drugs to expand access programs since the plants are not equipped to produce drugs on a larger scale and it takes time to scale up production).

<sup>313</sup> *Id.*

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However, the success of providing increased access to experimental drugs will depend on the participation of drug companies, and more specifically, tailoring a program to offer enough incentives to drug manufacturers while not sacrificing patients' rights. Through the above-mentioned adaptations to the EAID proposal, the compassionate-use programs will be a success and have the potential to meet desperate patients' needs while being equally advantageous for drug companies. While Alliance's litigation has been and will continue to be futile in gaining access to experimental drugs, Alliance's dedication to advocating for their desperate patients might bring relief to the terminally ill in the form of a proposal from the FDA.