EXPANDED ACCESS: POLICY, REGULATORY AND LEGAL CONSIDERATIONS

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I. *Introduction*

Expanded access, which is also known as "compassionate use" is the use of an investigational medical product (not approved by the FDA) on a patient outside of a clinical trial.[1] The genesis of the expanded access program lies in the HIV/AIDS crisis in the year 1987 when the FDA established the open access program in response to lobbying from the advocacy group, Act Up, to provide 4,804 patients with the unapproved drug, AZT.[2] The debate was reinvigorated in 2001 after Abigail Burroughs, a 19 year old college student with head and neck cancer, passed away on June 9 of that year.[3] She had attempted to procure the cancer drug, Erbitux, which was approved for other oncologic indications, but was denied access by the FDA. Her father sued the FDA in the D.C. Court of Appeals in 2005, appealing an adverse district court decision, with the circuit court holding a Fifth Amendment due process interest of terminally ill patients to seek potentially life-saving investigational new drugs where there was no other treatment (although this judgment was subsequently vacated by the same circuit court *en banc* one year later, reinstating the district court judgment).[4] The FDA then responded to the court's decision against expanded access by publishing guidance in the Federal Register on August 13, 2009, to take effect exactly two months later, in which the FDA created three new categories for expanded access: (1) individual patient expanded access, (2) intermediate-size patient population expanded access, (3) and treatment IND's (or protocols) for widespread use/expanded access.[5]

Additionally, on the state level, beginning with Colorado in 2014, 34 states have enacted "right to try" laws in an effort to help patients get access to experimental drugs outside of the traditional clinical trial framework, while one state, Hawaii, has vetoed the "right to try law," and the law has at least been introduced in all other states (even though the laws have not actually helped any patients obtain experimental medicine yet).[6] This paper will explore the justifications for and against expanded access to investigational drugs for terminally ill patients, concluding that the FDA must tread very carefully to protect patients from drugs that are unlikely to be successful.

II. *Case Law*

In the wake of *Abigail Alliance v. von Eschenbach*, patients with terminal conditions and were left with even less hope as the D.C. Circuit Court held, "that 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."[7] The American Society for Clinical Oncology (ASCO) filed an *amicus curiae* brief in support of the FDA's decision in which they argued that granting terminally ill patients the right to experimental drugs could jeopardize the entire clinical trial landscape.[8] The court conducted an analysis to determine whether terminally ill patients had a substantive due process fundamental right under the *Washington v. Glucksberg* standard (a tripartite analysis of the nation's history, legal traditions, and practices).[9] *Glucksberg* was a case in which the Supreme Court determined that Washington state's prohibition against physicians aiding or causing a suicide did not violate the substantive due process rights of its citizens, who wanted to procure their assistance so that they could terminate their lives.[10] The court's analysis of the nation's history, legal traditions, and practice is worth repeating:

> "In keeping with those decisions, we conclude that the Alliance has not provided evidence of a right to procure and use experimental drugs that is deeply rooted in our Nation's history and traditions. To the contrary, our Nation's history evidences increasing regulation of drugs as both the ability of government to address these risks has increased and the risks associated with drugs have become apparent."[11]

The court also cited *Rutherford v. United States* to express concerns that unapproved drugs could hasten terminally ill patients' deaths: "Although terminally ill patients desperately need curative treatments, as *Rutherford* holds, their deaths can certainly be hastened by the use of a potentially toxic drug with no proven therapeutic benefit."[12]

Notably, there has been a long line of case law on the extent to which patients have the ability to control their medical decisions, going back over a century and continually revisited in the court system, the legislative process, and the regulatory interpretations. In *Union Pacific Railway Co. v. Botsford*, the Supreme Court held that an injured plaintiff was not required to acquiesce to the railroad's request that she undergo surgical evaluation of her injuries: "No right is held more sacred, or is more carefully

guarded by the common law, than the right of every individual to the possession and control of his own person, free from all restraint or interference of others unless by clear and unquestionable authority of law."[13] In *Schloendorff v. Society of New York Hospital*, Justice Cardozo, on behalf of the Northeastern District Court of New York held: "Every human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient's consent commits an assault, for which he is liable in damages" in regards to a plaintiff who underwent a surgery, despite her refusal, and who went on to develop gangrene infection, requiring amputation.[14] In *Cruzan v. Director, Missouri Department of Health*, the Supreme Court held that a patient must necessarily have the right to refuse medical treatment as a corollary to the doctrine of informed consent.[15] The "right to try" cases argue that if patients have the right to refuse treatment, they necessarily must also have the right to subject their bodies to treatment.

III. *Statutory Basis for the Clinical Trial Process*

The thalidomide drug crisis in the 1960's led to tens of thousands of babies being born across the globe with severe birth defects.[16] Fortunately, the U.S. was largely spared due to the wisdom and perseverance of Dr. Frances Kelsey, who insisted that the morning sickness drug not be approved until the company submitted adequate data to justify its safety.[17] This near miss paved the way for strengthening the FDA's ability to approve new drugs based on both *safety* and *efficacy* for the first time in 1962 with the congressional amendments to the Food, Drug, and Cosmetic Act (FDCA) of 1938, known as the Kefauver-Harris amendments.[18] The amendments required companies to submit safety and efficacy data from "adequate and well controlled investigations" under 21 U.S.C. § 355(d).[19] These amendments also authorized the FDA to approve human clinical trials via the investigational new drug application (IND), regulate drug advertising, inspect drug-manufacturing facilities, and regulate good manufacturing practices.[20] The amendments also required drug manufacturers to report adverse safety information about their products to the FDA.[21] The very creation of the clinical trial process in 1962 fostered the improvement of scientific rigor, which then catalyzed the development of a cutting-edge life science industry, presumably as a result of the generation of vast quantities of data.[22] The clinical trial process is

not simply a matter of protecting patients, it is also a fundamental conversation that scientists must have, so that they might generate the information they need to sustain innovation itself.

IV. *Clinical Trial Regulations*

The FDA codified the regulations for human clinical trials under 21 C.F.R. § 312.[23] There is no requirement that drug sponsors procure FDA approval to conduct pre-clinical testing (although they must exercise good laboratory practices and protect animal welfare).[24] Once a drug company demonstrates sufficient preclinical data based upon animal studies, the FDA will approve an investigational new drug application, authorizing the company to begin the first phase of testing on humans.[25] It is important to note here that the right patients are seeking under the *Abigail Alliance* case is the right to procure drugs that have completed phase I clinical testing, not the right to procure drugs that have not yet been approved for any human trials.[26]

The phase I clinical trial is extremely small, typically including only 20-80 people (either patients or healthy volunteers) with the goal of establishing metabolism, pharmacology, and side effects.[27] If possible, the phase I study is also designed to gain early evidence of effectiveness.[28] It cannot be stressed highly enough, however, that the purpose of phase I testing is not determining efficacy, but rather determining initial safety in humans. In evaluating the response rates in phase I studies of chemotherapeutic drugs, for example, the objective response rate is "exceedingly low (as low as 2.5%).[29] Additionally, one report suggests the expected success rate of cancer drugs in the phase I stage is just 6%.[30] Phase II studies are designed to evaluate the common short term side effects and risks, and effectiveness of the drug for the particular indication(s) in patients with the disease or condition under study.[31] These studies use a relatively small number of patients, typically no more than several hundred.[32] Once a phase II study has generated preliminary evidence to suggest that a drug is effective, a phase III study will recruit from several hundred to several thousand volunteers to gather additional safety and effectiveness data and confirm the benefits of the drug outweigh the risks.[33] Phase III studies will use a placebo for some patients if there is not a treatment available that works, which certainly could be the

case in some studies for patients with terminal illness.[34] Phase I and II studies, however, do not use placebos.[35]

V. *Clinical Trial Economics: High Costs and Mostly Failures*

The clinical trial process is a difficult one. A Tufts University Study, which admittedly has an industry funding bias, determined that the cost of a drug approval is between $2.5 and $2.6 billion.[36] The clinical trial phase of a successful drug will typically last between 6 and 11 years.[37] Success is elusive. Initial safety data permits most drugs to progress to phase II, with most drugs failing to demonstrate sufficient efficacy to move to phase three.[38] Specifically, of the drugs that commence phase I testing, less than 60% will make it to phase II testing, while less than 36% of drugs that begin phase II testing will begin phase III testing; overall, just 8% of new drugs, for which an IND is filed, will ever be approved.[39]

VI. *Expanded Access After Abigail Alliance*

a. *The FDA's Approach*

The FDA clearly took note of the ongoing Abigail Alliance litigation when it proposed new expanded access regulations in the Federal Register on December 14, 2006.[40] The regulations were finalized on October, 13, 2009.[41] Admittedly, the FDA had been under fire for quite some time for failing to promulgate regulations as Congress had already passed the Food and Drug Modernization Act of 1997 (FDAMA), which had amended the FDCA to specifically address expanded access to investigational drugs for treatment use.[42] The 2007 final rule established regulations for expanded access, which included three mandatory requirements.[43] The FDA limited the application of expanded access to patients with a serious or life threatening illness, and who lacked adequate treatment; the FDA also required a risk benefit calculation that this treatment was appropriate, and required that expanded access use would not impede the ability to continue investigations that would lead to marketing approval.[44] The FDA created three different patient population sizes, eligible for expanded access: individual, intermediate-size, and broad scale (treatment IND).[45]

Of crucial note, the FDA has applied increasingly more stringent requirements for these populations to ensure that the drug sponsor is actually pursuing a submission and not merely bypassing

the drug approval process. The single patient IND may be for emergency use and requires that the patient is unable to procure the drug under another IND or protocol; the intermediate size expanded access procedures require that the drug be in development (or a justification for why this is not the case, for both approved drugs and drugs not in development); while the treatment IND requires that the sponsor be actively seeking marketing approval with due diligence.[46]

In 2009, the FDA also promulgated regulations on charging patients for treatment they receive under the expanded access program.[47] Sponsors must receive preapproval from the FDA and demonstrate evidence of the potential for clinical benefits significantly beyond existing therapy, evidence that charging is necessary due to extraordinary cost to the sponsor, and evidence that charging will not interfere with the development of the drug.[48] Additionally, sponsors are only authorized to recover direct costs (and not indirect costs).[49] As the costs of expanded access may be quite high, these regulations will probably have the effect of incentivizing sponsors to actually provide the drugs to some patients, while at the same time restricting access for those who are economically disadvantaged. Of note, the charges for expanded access are most likely to be borne by the actual patient and not a third party payer, as the Center for Medicare and Medicaid Services (CMS) and private insurance companies typically only pay for drugs that have been approved by the FDA for at least one indication.[50] However, there are concerns that even with the ability to charge, drug sponsors will not be sufficiently motivated to provide expanded access.[51]

b. *Other Legislative Proposals*

One approach put forward by policy advocates is a policy of open access for terminally ill patients with no regulation by the FDA.[52] The theory is essentially that terminally ill patients should have the right to personal autonomy.[53] This theory is almost a carbon copy restatement of the Abigail Alliance position that the D.C. Court of Appeals rejected on constitutional grounds.[54] The argument for open access anticipates the counter-argument that clinical trials are necessary for drug approval by indicting the entire clinical trial process as one that generally fails to deliver safe and effective drugs based on the dismal success rates of new drug candidates.[55]

A second, more modest approach is a compromise approach between open access to drugs and FDA oversight of the expanded access program. Following the Abigail Alliance decision in 2007, the Access, Compassion, Care, and Ethics for Seriously Ill Patients (ACCESS) Act was introduced in the Senate by Sam Brownback (Republican) and by Diane Watson (Democrat) in the House of Representatives in 2008.[56] Both bills failed to progress beyond the committee level. The ACCESS Act proposed modifying the FDCA Act to include a new category for expanded access approval, known as "Compassionate Investigational Access," in which drug sponsors could obtain marketing approval after phase I investigations with just preliminary evidence of effectiveness, which was allowed to come exclusively from animals.[57] This would have been an entirely new category of approval, which was only available for terminally ill patients who had exhausted other options; the drug company would still have been required to submit an NDA for full marketing authorization for other patients.[58] Patients would have been required to waive all causes of action against the drug manufacturer in order to be eligible for the compassionate investigational access category of approved drugs.[59] In Congressional Record Proceedings, Sam Brownback clarified that this category of access did not require that patients have *exhausted* or even *tried* every existing treatment, instead requiring only that patients have *examined* all existing treatments, which would be a deviation from existing expanded access regulations.[60]

While the ACCESS Act appears tempting at first glance, there are two extreme dangers of this approval process. The first concerns safety and efficacy, while the second concerns the high cost to society of this policy. The ACCESS Act would explicitly not have required any efficacy data in humans, instead only requiring animal efficacy data.[61] Additionally, the safety data would have only been based on short term dose studies of phase I testing, which may involve as few as twenty healthy volunteers.[62] Notably, there have been high profile cases of treatments being prematurely used on patients where the treatment dramatically worsened outcomes, most significantly with high dose chemotherapy, combined with autologous bone marrow transplantation in breast cancer patients – a treatment which accelerated the deaths of sixty-five patients, as compared to four in a control group with traditional therapy.[63] Other reports noted the relatively high rate of the appearance of success in oncology trials in phase I and II,

compared to other drug categories, combined with the relatively high rate of failure in phase III, relative to other drugs.[64] Policymakers must avoid giving false hope to patients who are terminally ill. The second criticism concerns the dangers to society of creating this category. For example, it could be difficult for the FDA to define what a terminally-ill patient is, leading to an unintended expansion of this category beyond patients who are considered terminally-ill by conventional standards.[65] Additionally, the immunity provisions of this bill could over-incentivize pharmaceutical companies to utilize this category.[66] Drug companies may submit much riskier products through this channel, knowing that patients have no recourse if the drug turns out to be dangerous.[67] They may also drag their feet on seeking further approval, understanding that those approvals both expose them to liability and cost quite a bit more in clinical trials costs.[68] These approvals could also slow down the FDA's approval process of other drugs as the FDA shifts resources to compassionate investigational use approvals.[69]

Ultimately, Congress decided to utilize an approach, far more deferential to the FDA with the passage of the 21st Century Cures Act, which was signed into law on December 13, 2006.[70] The law responded to the expanded access issue in two ways, with the second being the far more long-reaching response: (1) drafting new expanded access policies to be implemented by the FDA and pharmaceutical companies; (2) expanding funding for medical research and accelerating approval times.[71] The expanded access policy is quite weak, requiring only that makers of investigational drugs publish their policies for expanded access, without expanding FDA authority to regulate expanded access or obligating pharmaceutical companies to provide expanded access.[72] Presumably, the theory is that by increasing transparency more people will be able to access these treatments. The law created a new, accelerated approval category for regenerative therapies and a summary level review category (i.e., submission of an application for drug approval without full clinical trial data) for supplemental new drug applications.[73] Both of these accelerated pathways will speed up the approval of treatments for patients with terminal illnesses, either by expanding uses of existing drugs or by generating the innovation of novel, regenerative treatments. Most significantly, the 21st Century Cures Act authorized $4.8 billion in funding for the NIH over ten years to research precision medicine, brain diseases, and cancer.[74] While the

authorization of funding could have a dramatic impact on the funding of medical research, which could lead to dramatic advances in medicine, it is important to note that authorization does not mean appropriation. In fact, the Trump administration has proposed a 2017-2018 budget which does the exact opposite, slashing funding to the NIH by 18.3%, or about $5.8 billion, in just one tenth of the time![75] Additionally, the 21st Century Cures Act funding has been made possible by $3.5 billion in cuts from the Prevention and Public Health Fund (among other savings elsewhere).[76] There are concerns that this shift in funding could do more harm than good to public health.

VII. *Right To Try Laws Revisited: The State-level Approach*

Despite the fact that 34 states have enacted right-to-try laws, no patients have yet benefitted from these laws.[77] Some commentators suspect that the goal is to create a federal right to try law by shifting public opinion to force Congress' hand.[78] These laws do not circumvent federal law, but instead merely create a state right.[79] Additionally, the FDA has yet to take an official position on these laws.[80] Presumably, the FDA may choose not to enforce its regulations where states have chosen to legislate, as in the case of marijuana legalization.[81] However, the stakeholders here are different. Marijuana growers have a strong financial interest in selling marijuana in U.S. states, while pharmaceutical companies have virtually no incentive to circumvent the FDA regulations, as the FDA specifically sets out cost limitations for the amount these companies can charge patients for their drugs under expanded access price regulations.[82] Additionally, the FDA has ample sanctions against drug manufacturers at its disposal, including debarment, which can provide a lifetime bar on pharmaceutical company employees who attempt to circumvent the FDA's regulations.[83] Potentially, citizens of states with right to try laws may attempt to procure drugs for personal use, citing right to try laws.[84] The FDA's personal importation policy, however, does not authorize people to circumvent FDA laws.[85] Additionally, the policy applies only to foreign drugs that are not domestically available, so it does not complement the FDA's expanded access regulations as those drugs, presumably, would be available domestically under an expanded access category if the company so chose.[86] Right to try laws appear to be far more symbolic than substantive at this point, although this could change if the public sentiment catalyzes some type of policy change.

VIII. *Conclusion*

Expanded access is an uncomfortable topic to discuss as it is fraught with a sense of paternalism. Throughout the history of the United States, patients have sought – and been granted – increasing autonomy over their bodies. This has not come without a cost, of course, as many treatments have accelerated the deaths of these terminally ill patients. The right that has been sought is essentially the right to try drugs that have not been tested or have been subject to minimal levels of safety evaluation. Most of these drugs ultimately will not be approved because they are simply unsafe or they are ineffective. There have been various movements in state legislatures and in the United States Congress following the D.C. Court of Appeals holding in the *Abigail Alliance* case that terminally ill patients have no right to potentially-life saving unapproved drugs. The FDA has created new categories for expanded access; these will surely expand access for patients. Nineteen year old Abigail Burroughs, of course, did not have access to these categories before her death in 2001. There may lay some hope for terminally ill patients, however, with the 21st Century Cures Act, provided that Congress does appropriate the medical research funds which the Act authorized and provided that those outlays do generate innovative treatments, which are safe and effective. The real solution is probably not a desperate grab by a patient for something… anything… that might work, which is the right they are seeking under expanded access reform. The practice of medicine is complex; physicians are in the best position to make medical decisions. As a society, however, we need to empower physicians and patients by investing in the research that generates these new treatments in the first place, by submitting these treatments through clinical trials that confirm they do, in fact, provide an adequate treatment for the patients, who deserve nothing less than a rigorous investment in genuinely safe and effective medicines.

[1] U.S. Food & Drug Admin., "Expanded Access (Compassionate Use)" (Apr. 4, 2017), https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/.

[2] U.S. Food & Drug Admin., "Expanded Access and Expedited Approval of New Therapies Related to HIV/AIDS" (Aug. 7, 2014), https://www.fda.gov/ForPatients/Illness/HIVAIDS/Treatment/ucm134331.htm; Darshak M. Sanghavi, *The Pills of Last Resort* N.Y. TIMES (Oct. 31, 2013), https://mobile.nytimes.com/2013/11/03/magazine/how-dying-patients-get-access-to-experimental-drugs.html?from=magazine&_r=0.

[3] Abigail Alliance, "Our Story" (2009), http://www.abigail-alliance.org/story.php.

[4] Abigail Alliance v. von Eschenbach, 445 F.3d 470, 484-85(D.C. Cir. 2006), *vacated* 495 F.3d 695, 713 (D.C. Cir. 2007).

> "If there is a protected liberty interest in self-determination that includes a right to refuse life-sustaining treatment, even though this will hasten death, then the same liberty interest must include the complementary right of access to potentially life-sustaining medication, in light of the explicit protection accorded 'life.'"

[5] 74 Fed. Reg. 40,900 (Aug. 13, 2009); U.S. Food & Drug Admin., *Expanded Access to Investigational Drugs for Treatment Use —Questions and Answers Guidance for Industry* (June 2016), https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm351261.pdf.

[6] Righttotry.org, http://righttotry.org/ (last visited April 20, 2017); Julie Turkewitz, *Patients Seek 'Right to Try' New Drugs* N.Y. TIMES (Jan. 10, 2015), https://www.nytimes.com/2015/01/11/us/patients-seek-right-to-try-new-drugs.html?_r=1

> "The laws do not seem to have helped anyone obtain experimental medicine, as the drug companies are not interested in supplying unapproved medications outside the supervision of the F.D.A. But that seems almost beside the point to the Goldwater Institute, the libertarian group behind legislative efforts to pass Right to Try laws. 'The goal is for terminally ill patients to have choice when it comes to end-stage disease,' said Craig Handzlik, state policy coordinator for the Goldwater Institute, based in Arizona. 'Right to Try is something that will help terminally ill people all over the country.'"

[7] Abigail Alliance v. von Eschenbach, 495 F.3d 695, 713 (D.C. Cir. 2007), *cert denied* 552 U.S. 1159 (2008).

[8] Brief for the Am. Soc'y Clinical Oncology et al. as Amici Curiae Supporting Appellees at 19-22, Abigail Alliance v. Von Eschenbach, 495 F.3d 695 (D.C. Cir. 2007).

[9] Washington v. Glucksberg, 521 U.S. 702, 720-21, 117 S.Ct. 2258, 138 L.Ed.2d 772 (1997)

> "First, we have regularly observed that the Due Process Clause specially protects those fundamental rights and liberties which are, objectively, deeply rooted in this Nation's history and tradition and implicit in the concept of ordered liberty, such that neither liberty nor justice would exist if they were sacrificed. Second, we have required in substantive-due-process cases a careful description of the asserted fundamental liberty interest."

[10] *Id.*

[11] *Id*. at 711.

The court also rejects other arguments raised by the Abigail Alliance:

> "Similarly, our legal traditions of allowing a necessity defense, prohibiting intentional interference with rescue, and recognizing a right of self-defense cannot justify creating a constitutional right to assume any level of risk without regard to the scientific and medical judgment expressed through the clinical testing process."

[12] *Id*. at 713, *citing* Rutherford v. U.S. 616 F.2d 455 (10th Cir. 1980). Interestingly, Rutherford involved the same drug that Steve McQueen took in Mexico, which may have played a role in accelerating his death. *See, e.g.*, Barron H. Lerner, *McQueen's Legacy of Laetrile* N.Y. TIMES (Nov. 5, 2005), http://www.nytimes.com/2005/11/15/health/mcqueens-legacy-of-laetrile.html.

[13] Union Pac. Ry. Co. v. Botsford, 141 U.S. 250, 251 (1891).

[14] Schloendorff v. Soc'y of N.Y. Hosp., 105 N.E. 92, 93 (N.Y. 1914).

[15] Cruzan v. Dir., Mo. Dep't. of Health , 497 U.S. 261, 270 (1990).

[16] Margaret Hamburg, *50 Years After Thalidomide: Why Regulation Matters* FDA VOICE (Feb. 7, 2012), https://blogs.fda.gov/fdavoice/index.php/2012/02/50-years-after-thalidomide-why-regulation-matters/.

[17] *Id.* Notably, the company marketing thalidomide had not even conducted studies on pregnant animals!

[18] Pub.L. No. 87-781, 76 Stat. 780 (1962); Hamburg, *supra* note 16.

> "The tragedy of thalidomide led to changes that strengthened both the regulatory and scientific environment for medical product development and review.

> In response to the public uproar, in 1962 Congress enacted the Kefauver-Harris amendments to the Federal Food, Drug and Cosmetic Act. Thanks to these new amendments, manufacturers had to prove that a drug was not only safe, but also effective. Approvals had to be based on sound science. Companies had to monitor safety reports that emerged postmarket and adhere to good manufacturing practices that would lead to consistently safe products. And there were new protections for patients."

[19] 21 U.S.C. § 355 (d).
[20] 21 U.S.C. §§ 360a-1, 352, 374, 351, 355 (k).
[21] *Id*.
[22] Hamburg, *supra* note 16.

> "The amendments not only benefited patients, they helped industry, raising scientific standards that eventually ushered in today's sophisticated, science-based life sciences industry.
>
> For the very first time, many companies put in place research and development programs, including the design and implementation of controlled clinical trials. Major therapeutic breakthroughs resulted."

[23] Investigational New Drug Applications, 21 C.F.R. Part 312.
[24] Good Laboratory Practice for Nonclinical Laboratory Studies, 21 C.F.R. Part 58.
[25] 21 C.F.R. §§ 312.2(a), 312.40, 312.20.
[26] Abigail Alliance, *supra* note 7 at 699. "Accordingly, the Alliance requested that the FDA promulgate new regulations that would allow sponsors to market experimental drugs, under some circumstances, after the completion of Phase I trials."
[27] Phases of an Investigation 21 C.F.R. § 312.21(a).
[28] *Id*.
[29] Craig Umscheid et al., *Key Concepts of Clinical Trials: A Narrative Review* POSTGRAD MED. (Sept. 2011), at 5, *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3272827/pdf/nihms-350738.pdf.
[30] Peter D. Jacobson & Wendy E. Parmet, *A New Era of Unapproved Drugs: The Case of Abigail Alliance v. Von Eschenbach*, 297 J. AM. MED. ASS'N. 205, 206 (2007).
[31] Phases of an Investigation 21 C.F.R. § 312.21(b).
[32] *Id*.
[33] Phases of an Investigation 21 C.F.R. § 312.21(c).
[34] American Cancer Society, *What Are the Phases of Clinical Trials* (2017), https://www.cancer.org/treatment/treatments-and-side-effects/clinical-trials/what-you-need-to-know/phases-of-clinical-trials.html
[35] *Id*.
[36] Joseph A. DiMasi, et al. *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, TUFTS UNIV. (Nov. 18, 2014), http://csdd.tufts.edu/files/uploads/Tufts_CSDD_briefing_on_RD_cost_study_-_Nov_18,_2014..pdf (funded in part by PhRMA).
[37] *Joseph A. DiMasi et al. The Price of Innovation: New Estimates of Drug Development Costs* J. HEALTH ECON. (2003) 151–85.
[38] DiMasi, *supra* note 37.
[39] *Id*.
[40] 71 Fed. Reg. 71,240 (Dec. 14, 2006); U.S. Food & Drug Admin., *Expanded Access to Investigational Drugs for Treatment Use*, https://www.fda.gov/OHRMS/DOCKETS/98fr/06-9684.pdf.

> "The Food and Drug Administration (FDA) is proposing to amend its regulations on access to investigational new drugs for the treatment of patients. The proposed rule would clarify existing regulations and add new types of expanded access for treatment use. Under the proposal, expanded access to investigational drugs for treatment use would be available to individual patients, including in emergencies; intermediate size patient populations; and larger populations under a treatment protocol or treatment investigational new drug application (IND). The proposed rule is intended to improve access to investigational drugs for patients with serious or immediately life-threatening diseases or conditions, who lack other therapeutic options and who may benefit from such therapies."

[41] 74 Fed. Reg. 40,900 (Aug. 13, 2009); U.S. Food & Drug Admin., *supra* note 5.

[42] Expanded Access to Unapproved Therapies and Diagnostics, 21 U.S.C. 360bbb (2017); Food and Drug Administration Modernization Act of 1997 (FDAMA), Pub. L. No. 105-115; Federal Food, Drug, & Cosmetic Act § 571 (1938, *amended* 1997).

[43] Requirements for all expanded access uses, 21 C.F.R. § 312.305

> "(1) The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;
>
> (2) The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and
>
> (3) Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use."

[44] *Id*.

[45] 21 C.F.R. §§ 312.310, 312.315, 312.320.

[46] *Id*.

[47] Charging for investigational drugs under an IND, 21 C.F.R. § 312.8.

[48] *Id*.

[49] Charging for investigational drugs under an IND, 21 C.F.R. § 312.8 (d)(i)

> "Direct costs are costs incurred by a sponsor that can be specifically and exclusively attributed to providing the drug for the investigational use for which FDA has authorized cost recovery. Direct costs include costs per unit to manufacture the drug (e.g., raw materials, labor, and nonreusable supplies and equipment used to manufacture the quantity of drug needed for the use for which charging is authorized) or costs to acquire the drug from another manufacturing source, and direct costs to ship and handle (e.g., store) the drug."

[50] Covington & Burling, *FDA's Final Rules Regarding Expanded Access and Charging for Investigational Drugs and CMS Payment Implications* (Aug. 26, 2009) (Food & Drug E-Alert), https://www.cov.com/-/media/files/corporate/publications/2009/08/fdas-final-rules-regarding-expanded-access-and-charging-for-investigational-drugs-a.pdf.

[51] Seema Shah & Patricia Zettler, *From a Constitutional Right to a Policy of Exceptions: Abigail Alliance and the Future of Access to Experimental Therapy*, 10 YALE J. OF HEALTH POLICY, LAW, AND ETHICS (Mar. 3, 2013) 135, 174 "it is not clear that an ability to recover costs is the major bottleneck impeding access to unapproved therapy."

[52] *Id*. at 175.

> "A few scholars have argued for open access, in which patients may elect to take any unapproved drug that a company will provide and the FDA does not regulate expanded access at all. Open access supporters have acknowledged that most unapproved drugs are eventually proven ineffective or unsafe. However, they argue that an open access model does not threaten the state's interest in promoting public health because the state's interest is limited when 'the individual is terminally ill.' Moreover, proponents of open access contend that the clinical trials process fails to achieve the public health goal of producing a market of safe and efficacious drugs. Consequently, they argue that the emphasis of the expanded access debate should not be on the state's public health interests but on the importance of patient autonomy. Open access supporters claim that patients are the best parties to decide whether an unapproved drug is an appropriate treatment and in their best interests."

[53] *Id*.

[54] Abigail Alliance, *supra* note *7* at 703.

> "Looking to whether the Alliance has demonstrated that its right is deeply rooted in this Nation's history, tradition, and practices, the Alliance's claim for constitutional protection rests on two arguments: (1) that 'common law and historical American practices have traditionally trusted individual doctors and their patients with almost complete autonomy to evaluate the efficacy of medical treatments'; and (2) that FDA policy is 'inconsistent with the way that our legal tradition treats persons in all other life-threatening situations.' More specifically, the Alliance argues that the concepts of self-defense, necessity, and interference with rescue are broad enough to demonstrate the existence of the fundamental right they seek-a right for 'persons in mortal peril' to

'try to save their own lives, even if the chosen means would otherwise be illegal or involve enormous risks.'"

[55] Shah *supra* note 51 at 175.

[56] Access, Compassion, Care, and Ethics for Seriously Ill Patients Act of 2008, S.R. 3046, H.R. 6270, 110th Cong. (2008).

[57] *Id*. at § 4(A)

> "A sponsor of an investigational drug, biological product, or device applying for Compassionate Investigational Access approval of the product shall submit to the Secretary a notice of claimed exemption under section 505(i) or 520(g), as applicable, (referred to in this subsection as an 'application for Compassionate Investigational Access'), which shall contain—
>
> (i) data and information from completed Phase I clinical investigations and any other nonclinical or clinical investigations;
>
> (ii) preliminary evidence that the product may be effective in humans against a serious or life-threatening condition or disease, which evidence may be 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, and may be based on a small number of patients or a subset of the patient population…"

[58] *Id*. at § 3

> "(8) PATIENT ELIGIBILITY FOR COMPASSIONATE ACCESS.—In order for a patient to access a product available through Compassionate Investigational Access, the physician must document in writing that the patient—
>
> (A) is seriously ill;
>
> (B) has exhausted all treatment options approved by the Secretary for the condition or disease for which the patient is a reasonable candidate; and
>
> (C) has unsuccessfully sought treatment or obtained treatment that was not effective, with an investigational drug, biological product, or device for which such individual is a reasonable candidate, which shall include consideration of a patient's ineligibility for participation in clinical trials, the lack of source of supply and geographic factors."

[59] *Id*. at § 3

> "(12) IMMUNITY.—
>
> (A) IN GENERAL.—A manufacturer, distributor, administrator, sponsor, or physician who manufactures, supplies, distributes or prescribes a product approved under an application for Compassionate Investigational Access shall be immune from suit or liability caused by, arising out of, or relating to the design, development, clinical testing and investigation, manufacture, labeling, distribution, sale, purchase, donation, dispensing, prescribing, administration, efficacy, or use of a drug, biological product, or device subject to an approved Compassionate Investigational Access application.
>
> (B) CLAIMS.—No claim or cause of action against a manufacturer, distributor, administrator, sponsor, or physician who manufactures, supplies, distributes or prescribes a product subject to an approved Compassionate Investigational Access application shall exist in any Federal or State court for claims of property, personal injury, or death caused by, arising out of, or relating to the design, development, clinical testing and investigation, manufacture, labeling, distribution, sale, purchase, donation, dispensing, prescribing, administration, efficacy, or use of a drug, biological product, or device subject to an approved Compassionate Investigational Access application. Any such claim or cause of action that is filed in Federal or State court shall be immediately dismissed."

[60] 154 Cong. Rec. 16, 695 (2008).

[61] ACCESS Act, *supra* note 56 at § 4(A).

[62] *Id*.; Phases of an Investigation 21 C.F.R. § 312.21(a).
[63] Shah *supra* note 50 at 178-79 (citing Cynthia M. Farquhar et al., *High Dose Chemotherapy for Poor Prognosis Breast Cancer: Systematic Review and Meta-Analysis*, 33 CANCER TREATMENT REVS. 325 (2007); Michelle M. Mello & Troyen A. Brennan, *The Controversy Over High-Dose Chemotherapy with Autologous Bone Marrow Transplant For Breast Cancer*, 20 HEALTH AFF. 101 (2001); H.G. Welch & J. Mogielnicki, *Presumed Benefit: Lessons from the American Experience with Marrow Transplantation for Breast Cancer*, 324 BRIT. MED. J. 1088 (2002)).
[64] Bruce Booth, Robert Glassman & Philip Ma, Oncology's Trials, 2 NATURE REVS. DRUG DISCOVERY 609, 609 (2003).
[65] Shah *supra* note 51 at 181-86.
[66] *Id*.
[67] *Id*.
[68] *Id*.
[69] *Id*.
[70] 21st Century Cures Act, Pub. L. No. 114-255.
[71] 21st Century Cures Act, Pub. L. No. 114-255 §§1001, 3031, 3032, 3033
[72] *Id*. at § 3032.
[73] *Id*. at §§ 3031, 3033.
[74] *Id*. at §2001.
[75] Harold Varmus, *Why Trump's NIH Cuts Should Worry Us*, N.Y. TIMES (Mar. 22, 2017), https://www.nytimes.com/2017/03/22/opinion/why-trumps-nih-cuts-should-worry-us.html.
[76] *See, e.g.*, Sheila Kaplan, *Senate Passes Landmark 21st Century Cures Act — But It Will Take Years to Implement*, STAT (Dec. 7., 2016), https://www.statnews.com/2016/12/07/21st-century-cures-senate-passes/.
[77] Righttotry.org, Julie Turkewitz,*supra* note 6.
[78] *See, e.g*.,Sam Adriance, *Fighting for the "Right To Try" Unapproved Drugs: Law as Persuasion*, 124 YALE LAW J.(Dec. 4, 2014) (online forum).
[79] *Id*.
[80] *Id*.
[81] *Id*.
[82] *Id*.; Charging for investigational drugs under an IND, 21 C.F.R. § 312.8 (d)(i).
[83] *See, e.g.*, Tamar Nordenberg, *Inside FDA: Barring People from the Drug Industry*, FDA, https://www.fda.gov/ICECI/EnforcementActions/FDADebarmentList/ucm139627.htm

> "'Some may object that the bill is unduly harsh, but let us not forget, this bill is only aimed at those who have engaged in criminal misconduct, those who put corporate profits ahead of public safety.'
> --Generic drug company representative Kip Schwartz, testifying before Congress about debarment.
>
> For putting unlawful profit ahead of consumer safety, 38 drug industry employees are facing a lifetime bar on practicing their livelihood. They were convicted, under the Federal Food, Drug, and Cosmetic Act, of felonies that included submitting false data to the Food and Drug Administration, lying to FDA investigators, paying or accepting bribes, and selling prescription drug samples. As a result, the 38 were "debarred" by FDA from working for a drug company."

[84] FDA, Personal Importation Policy (PIP), Frequently Asked Questions (FAQs), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/ImportsandExportsCompliance/UCM297909.pdf, last accessed April 22, 2017.

> "Q. What is the Personal Importation Policy?
> A. The Personal Importation Policy, also known as the PIP, is a guidance that sets forth FDA's enforcement priorities related to the personal importation of drugs that are not FDA approved and, therefore, are in violation of the Federal Food, Drug, and Cosmetic Act (FDCA) and subject to enforcement action. FDA recognizes there are circumstances under which a United States citizen may wish to seek treatment with an unapproved drug that is not domestically available, or a foreign citizen traveling to the United States may wish to continue treatment with a foreign drug that is not domestically available. The PIP was developed to address such circumstances and gives FDA instructions on exercising its

enforcement discretion to permit importation of drugs otherwise considered illegal in the United States. In determining whether exercise discretion is warranted, FDA considers the following factors:

- The drug must be unapproved and intended for use in a serious medical condition for which there is no effective treatment domestically available
- There must be no commercialization or promotion of the drug in the United States
- The drug cannot represent an unreasonable health risk to the patient
- The request must be accompanied by an affirmation that the drug is for the patient's use only and by the name and address of the United States–licensed physician responsible for the patient's treatment
- The request is generally for no more than a 3-month supply of the drug

The PIP does not give a license to individuals to import unapproved drugs for personal use into the United States. It does not change the law or create or confer any legally enforceable rights, privileges, or benefits on or for any individual, and it does not bind the FDA or the public."

[85] *Id.*
[86] *Id.*