

The Expanded Access Cure: A Twenty-First Century Framework for Companies

Stacey B. Lee¹ · Alexandra Y. Murata²

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Abstract Through expanded access protocols, the Food and Drug Administration (FDA) allows patients with serious or immediately life-threatening diseases access to experimental drugs outside the clinical trial setting when no satisfactory alternative treatment is available. While the FDA has established a mechanism for providing patients with unapproved drug access, the regulations do not require the pharmaceutical company to provide the drug. The drug company's permission to use its experimental drug is a necessary prerequisite to using the FDA's expanded access mechanism. Increasingly, drug companies are coming under scrutiny regarding the programs governing that decision-making power. Historically, disclosing whether a company has an expanded access program, and whether or how it would respond to an expanded access request, has been left to discretion of the drug companies themselves. Few manufacturers publish adequate expanded access protocols. As a result, patients were provided with little insight into how companies evaluate expanded access requests and are naturally skeptical as to the ethical integrity of the process. The recently passed 21st Century Cures Act changes that practice by requiring drug companies to have, and make publically available, their expanded access procedures including criteria for evaluating and responding to patient requests. In this article, we contend that complying with the new

transparency provisions will require drug companies to respond to several unresolved expanded access issues. Namely, how to reconcile a patient's desire to access life-saving experimental therapies alongside the company and society's interest in the efficient development of new drugs. Even more challenging, how can companies devise practices for evaluating and processing expanded access requests that also fairly and equitably acknowledge those concerns? In addressing these questions, this article explores the legal, regulatory, business, and societal influences that have shaped expanded access policies and practices. From there, we provide companies a framework that balances appropriately the desires of individuals and gaining the requisite approvals ensure access not just for one person but for society.

Keywords Expanded access · Compassionate use · Corporate frameworks · Experimental drugs · Investigational drugs · FDA · Pharmaceutical manufacturers · Resource allocation

Introduction

You have been diagnosed with a terminal disease and have less than six months to live. There are no Food and Drug Administration (FDA)-approved treatments. Your physician informs you of an experimental drug that could save your life. The drug is in clinical trials; however, you are too sick to qualify. It will take approximately ten more years before the drug is available to the public. Your last possible chance for survival hinges on the drug company's willingness to make its experimental drug available to you.

Scenarios like this place drug companies under increased pressure to provide rapid access to unapproved drugs to treat life-threatening conditions when no other

✉ Stacey B. Lee
Staceyb.lee@jhu.edu
Alexandra Y. Murata
Amurata1@jhu.edu

¹ Johns Hopkins Carey Business School, 100 International Drive, Baltimore, MD 21202, USA

² Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, Baltimore, MD 21205, USA

treatment options exist. Through expanded access protocols, severely and terminally ill patients can request access to experimental drugs outside of a clinical trial setting. There are three categories of expanded access request. The most common request is for individual use, including emergency use. The second request is for intermediate patient populations that range from tens to hundreds of patients, and the final category includes requests for widespread treatment access.¹ This article focuses on individual patient requests.

The first step in the individual expanded access process requires the patient's physician to contact the drug company to obtain a letter of authorization verifying permission to use the experimental drug. Drug companies are under no obligation to provide the drug. While some drug companies will grant access, others will refuse a request for a number of reasons including: lack of sufficient supply of the drug, the patient is eligible to enroll in a clinical trial, or in some cases, provide no reason at all. If the company agrees, the physician then submits a request to the FDA for expanded access approval. The FDA grants over 99% of expanded access requests.²

Patients criticize drug companies for failing to clearly indicate their policies regarding expanded access. Patients have noted that for many experimental drugs, they cannot determine the company's expanded access policy, or for that matter, if one even exists. Other patients note that some drug companies fail to respond to their expanded access requests, leaving patients unsure as to the status of their request and their ability to access the experimental treatment. As a result, patients are turning increasingly to social media campaigns, Right to Try laws, and direct appeals take out with and use "to" with the drug companies in an effort to influence the granting of their requests.

In an effort to dispel the opacity surrounding drug companies' expanded access practices, on December 13, 2016, Congress enacted the 21st Century Cures Act (Cures Act) (Fig. 2). This federal legislation requires manufacturers of experimental drugs for serious or life-threatening diseases to make their policies publicly available regarding how they evaluate and respond to expanded access requests. Specifically, companies must make available: (1) contact information to facilitate communication about requests; (2) procedures for making expanded access requests; (3) general criteria used to evaluate requests; and (4) the length of time anticipated to knowledge receipt of requests.³

To comply with the Cures Act's transparency requirements, this article contends that drug companies will have to address one of the more daunting challenges in expanded

access practices. Drug companies will have to craft a framework for evaluating expanded access requests that appropriately balance company and societal interests in the efficient development of new drugs alongside a patient's desire to access lifesaving experimental therapies. Striking that balance necessitates an understanding of the legal, regulatory, business, and social factors that have influenced expanded access practices. Accordingly, this article examines key legal decisions, FDA regulations, Right to Try laws, and social media activity that have been significant in the evolution of expanded access. In addition, to assess the potential impact of the Cures Act and the level of transparency in drug companies' expanded access practices, this article analyzed data gathered from the web sites of 100 publicly traded pharmaceutical and biotechnological companies. Using these data, we determined how many of the companies included expanded access policies and identified the specific criteria of these posted expanded access policies. From here, the article sets forth a framework for companies to evaluate expanded access requests.

Expanded Access: The Informal Years—1962 Through the Late 1980s

The history of drug companies working with the FDA to provide patients access to experimental treatments outside of clinical trials dates back to 1962. In the absence of written regulations governing the process, the relationships were unofficial and the process was conducted primarily by the telephone. Physicians of severely and terminally ill patients who had no recourse other than an experimental drug called the FDA and requested access to that drug. Medical officers in the agency evaluated each situation individually and either approved or denied the request. The criteria for access to experimental drugs was simple, and approval required four basic elements: a drug company willing to supply the drug, a physician willing to prescribe it, the patient willing to give informed consent, and some basis for believing that the treatment was not an outright fraud or poison.⁴ Through these relaxed pathways, drug companies acting as sponsors agreed to make their experimental drugs available to patients outside of the clinical trial process.⁵ Early examples of patients who received pre-approval access to experimental drugs include: several thousands of patients with bronchospastic lung disease received metoprolol, patients with life-threatening arrhythmias received tocainide and mexiletin, and 20,000 vasospastic angina patients received calcium antagonists. Throughout the 1960s and 1970s, the FDA used this

¹ 21 C.F.R. §312.310; 21 C.F.R. §312.315, 21 C.F.R. §312.320.

² 21 CFR §312.310.

³ Pub. L. No. 114-255 (2016).

⁴ Nichols (1991).

⁵ Young et al. (1988).

straightforward process to provide thousands of patients access to experimental cardio selective beta-blockers.⁶

The onset of the AIDS crisis in the 1980s fundamentally altered the informal expanded access practices that drug companies and the FDA had used for nearly 20 years. As the epidemic raged unchecked, drug sponsors, HIV/AIDS patients, and patient advocate organizations urged the FDA to create a set of more formal procedures for expedited access to experimental drugs. Proponents for early access argued that even the most remote possibilities for improvement offered by experimental treatments may provide enormous benefit to the patient.⁷ While pro-early access groups waited for a formalized regulatory pathway to expedite access to experimental treatments, drug companies continued participating in the FDA's informal approval practice allowing patients access to experimental drugs outside of the clinical trial process.

At this time, patients with AIDS began suffering from inflammation of the retina and blindness caused by cytomegalovirus (CMV), which was considered to be an untreatable condition. In 1984, Syntex, a California based drug company received an urgent request to provide pre-approval access to treat a patient with ganciclovir, a drug believed to potentially work against CMV. While animal studies had yet to be completed and Syntex was years away from launching human trials, laboratory results showed promising results in treating CMV. The requesting physician stressed that he needed to begin treatment within the next 24 h or that it would be too late. Syntex agreed to provide the drug and scrambled to prepare all the necessary documents for release. Within 18 h of making the request, Syntex completed the necessary documentation, the FDA authorized administration, and the patient received ganciclovir. While the patient died of unassociated complications 4 days later, scientists determined that ganciclovir targeted the CMV infection. Within weeks, the company began to receive calls from around the USA to access ganciclovir.⁸

In response to the demand, Syntex decided it was the company's ethical obligation to continue to make drug available when requested and to provide it free of charge. To better manage and evaluate requests, Syntex quickly developed a written protocol that required patients to meet certain disease severity criteria. Patients had to produce a documented reason for immunocompromise and have an infection that was immediately threatening their life or eyesight. Due to the ganciclovir's effectiveness, Syntex did not feel that it could ethically justify performing the

double-blind clinical trials required by the FDA for approval. In 1988, Syntex applied for FDA approval to market ganciclovir based on data gathered from outside of clinical trials.⁹ The FDA's advisory committee rejected the application indicating that more data on the drug were needed. A few months later, the FDA announced that it was placing new restrictions on the drug to glean scientific data on ganciclovir's effectiveness and that it would no longer be available for treatment use (e.g., under an expanded access program).¹⁰

Amid mounting criticism from National Institutes of Health, advocacy groups, HIV/AIDS patients and the public, the FDA contacted Syntex. The agency indicated that it now wanted to approve ganciclovir as quickly as possible and requested Syntex reapply for approval and include any new available data. Three months later, the FDA approved ganciclovir and the drug was on the market by August 1989.¹¹

Other activity by companies to make their experimental drugs available to terminal or seriously ill patients included the Burroughs Wellcome laboratory of the Wellcome pharmaceutical enterprise.¹² In 1985, the laboratory sent azidothymidine (AZT), originally created to treat leukemia to the National Cancer Institute (NCI). AZT was the 11th drug tested in a shotgun approach against a virus soon known as HIV. In tests, the drug showed effectiveness in slowing down and preventing damage to the immune system, and reducing the risk of developing AIDS-related illnesses.¹³ The Burroughs Wellcome laboratory, working with NCI representatives and other federal agencies, created an "open-access clinical trial," which served as a way to release the drug free of cost to almost one-third of all AIDS sufferers in the USA and bypass the lengthy FDA approval process.¹⁴

Expanded Access: A Regulatory Approach—The Informal Becomes Formal

In 1987, primarily in response to the AIDS crisis, the FDA created a regulatory pathway that allowed large pools of severely and terminally ill patients to access experimental drugs outside of clinical trials. While these regulations increased access, patients, physicians, and pharmaceutical companies criticized the FDA for failing to include any expanded access mechanism authorizing individual

⁶ Young et al. (1988).

⁷ Eichler et al. (2013). The Risks of Risk Aversion in Drug Regulation, 12 *Nature*.

⁸ Buhles (2011).

⁹ Buhles (2011).

¹⁰ Kolata (1989).

¹¹ Buhles (2011).

¹² <http://www.bwfund.org/history>.

¹³ Sanghavi (2013).

¹⁴ Sanghavi (2013).

patients or anyone not part of a large group patient pool to access experimental drugs.¹⁵ In response to these concerns, in 2009, the FDA substantially revised the expanded access regulations. Current provisions allow individuals access to experimental drugs provided:

(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.¹⁶

The goal of the revised expanded access regulations was to provide more detail regarding all of the ways that patients may access experimental drugs. The FDA conceded that in the past, lack of clearly defined eligibility criteria and submission requirements created obstacles that prevented patients from accessing potentially beneficial experimental drugs.¹⁷ The new provisions sought to address those deficiencies as well as ease the administrative burden on physicians and companies willing to make their experimental drugs available. On a broader level, the FDA sought to create a framework that appropriately balances the FDA's interest in authorizing access to promising experimental drugs while protecting patient safety and ensuring the development of new drugs for market approval.¹⁸

Notwithstanding these efforts, provider, patient, and industry confusion regarding: what expanded access was; when it could be used; what information must accompany a request; and what role the FDA plays in determining the appropriateness of the request, remained. As a result, in 2013 and again in 2016, the FDA released draft guidance further clarifying the implementation of the 2009 regulations.¹⁹

As discussed, the primary objectives of expanded access regulations are to increase the availability of experimental drugs to patients with life-threatening illnesses while protecting patient safety and avoiding interference with the

development of investigational drugs for marketing under approved applications. In several areas, the revised regulations and industry guidance further that goal. According to the FDA, data from October 2009–September 2014 show that the FDA received an average of 1,206 expanded access requests a year and approved of 99.5% of them.^{20, 21}

Expanded Access: A Word from the Courts

United States v. Rutherford

In addition to drug company and regulatory efforts to make experimental drugs available outside of the clinic trial process, patients have turned to the courts in an effort to ensure a legal right of access to experimental drugs. The 1979 landmark case, *United States v. Rutherford*, raised the issue of whether terminally ill patients have a constitutional right to access potentially lifesaving experimental drugs.

In the case, patients and their spouses sued the FDA to enjoin it from barring pre-approval access to Laetrile. This experimental drug was available outside the USA and widely believed to be an effective cancer treatment. In ruling against the patients, the US Supreme Court found no express right of terminally ill cancer patients to access experimental drugs. The Court noted that the government (specifically the FDA) has an interest in regulating unsafe drugs and protecting the public's health.²² The Court deemed that "a drug is as unsafe for the terminally ill as for anyone else if its prospects of death and physical injury are not outweighed by its potential for benefit".²³ In *Rutherford*, the Court noted that the FDA had not yet found evidence that Laetrile was safe and effective. Accordingly, the Court determined the patients had no legally recognized right of access.²⁴ While the plaintiffs framed their right of access as a constitutional one, the Court declined to directly address that argument and based its decision on a statutory interpretation of the Federal Food, Drug, and Cosmetic Act.

Abigail Alliance v. von Eschenbach

In 2003, the Abigail Alliance (AbA), a patient advocacy group, sued the FDA for access to unapproved drugs.

¹⁵ Food and Drug Administration, HHS (2009).

¹⁶ 21 C.F.R. §312.305 (2105).

¹⁷ Food and Drug Administration, HHS (2009).

¹⁸ Food and Drug Administration, HHS (2009).

¹⁹ U.S. Department Health and Human Services (2013).

²⁰ US Food and Drug Administration (2013). IND Activity Reports. Expanded Access INDs and Protocols. <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/INDActivityReports/ucm373560.htm>.

²¹ Kim et al. (2015).

²² *United States v. Rutherford* (1979).

²³ Id. at 556.

²⁴ *United States v. Rutherford* (1979).

Similar to the *Rutherford* plaintiffs, the AbA grounded its claim on the premise that terminally ill patients have a fundamental right to experimental drugs. Here, the AbA asserted that the right applied to all drugs that have completed Phase I testing.²⁵ The district court rejected this argument and granted the FDA's motion to dismiss. On appeal, the court overturned the district court's ruling and ruled in favor of the AbA.²⁶ In doing so, the appellate court created a new fundamental right and eliminated the FDA's ability to prohibit patient access to experimental drugs prior to their approval.²⁷ In response to the newly created constitutional right, Dr. Peter Jacobson, a noted bioethicist from the University of Michigan School of Public Health, commented "This is an aggressively individualist view, one that breathtakingly slights the public's interests in drug safety, appeals to the rhetoric of choice and the belief that there is a medical cure for every illness".²⁸

Seeking to avoid a seismic reduction in its authority, the FDA immediately requested a rehearing before all of the judges of the court. During that *en banc* review, the U.S. Court of Appeals for the District of Columbia affirmed the district court ruling in favor of the FDA. In rejecting the reasoning of the appellate court panel, the U.S. Court of Appeals explicitly held that "there is no fundamental right...to experimental drugs for the terminally ill".²⁹ The AbA appealed the decision to the Supreme Court. In 2008, the Supreme Court declined to review the case, which left the FDA's authority and regulations in place and once again allowed the Court to sidestep directly addressing the constitutional implications in these cases.

As a legal issue, the question of whether or not patients can ground their arguments for access to unapproved drugs in the constitution is closed. However, outside of the courts remains the unanswered question of, what are the ethical dimensions of patient self-determination and autonomy? Due to the vital role that drug company practices play in making experimental treatments available, drug companies find that the public is increasingly looking to them to provide the answer. More specifically, drug companies have been left with the responsibility of striking the appropriate balance between a desire to respond to an individual's suffering and the need to ensure their products proceed through the regulatory processes for evaluating and approving drugs for the public.³⁰

For patients suffering from serious or terminal diseases, the Supreme Court's holding laid bare the very limited

nature of treatment options outside of a clinical setting. Recognizing expanded access as the most viable option, patients shifted their efforts to influence drug company experimental treatment practices. Patients began pressuring drug companies for increased and earlier access to experimental treatments. In addition, patients also began requesting access to the criteria that companies use to determine whether or not to make their drugs available in response to expanded access requests. What follows are recent events highlighting some of those efforts.

Expanded Access: Recent Defining Events

The Ebola Epidemic

In August 2014, the Ebola epidemic that ravaged West Africa was prominently featured in the US news after two American humanitarian workers contracted the virus. In an effort to save their lives, the pharmaceutical manufacturer MappBio made a limited amount of ZMapp, an unapproved experimental monoclonal antibody derived from mice, available.³¹ The media chronicled the Americans' treatment and attributed their healthy recovery to the availability of an experimental drug through the expanded access protocols.

Renewing issues raised, but left unresolved during the *Abigail Alliance* lawsuit, researchers and ethicists debated the appropriateness of treating patients with experimental drugs that had not been tested on humans or completed Phase I testing. Some researchers and ethicists argued against using experimental drugs outside of clinical trials.³² They stressed that to properly evaluate the effectiveness of an experimental therapy requires using the "gold standard" in clinical research, a randomized controlled trial. Researchers and ethicists on the other side of the debate argued that, given the lethality of the virus, the use of unapproved drugs outside of a clinical trial was not only permissible, but obligatory. Advocates of this approach stressed that in the absence of any known cure, ethics demanded the broadest dissemination of expanded access therapies.³³ Notably absent from the discourse, however, was a legal and ethical analysis of the decision-making process used by the drug companies and the FDA to determine whether to make the experimental drugs available outside of the clinical trial setting.

In the case of the American missionaries, the media presumed that the FDA had authorized the use of ZMapp and other experimental drugs through expanded access

²⁵ *Abigail Alliance v. von Eschenhach* (2007).

²⁶ *Abigail Alliance v. von Eschenhach* (2007).

²⁷ *Abigail Alliance v. von Eschenhach* (2007).

²⁸ Brower (2014).

²⁹ *Abigail Alliance v. von Eschenhach* (2007).

³⁰ Walker et al. (2014).

³¹ Qiu et al. (2014).

³² Rid and Emanuel (2014).

³³ Adebamowo et al. (2014).

protocols. The FDA, however, refuses to acknowledge what, if any role, it had played in the missionaries' access to the experimental treatments. Given that information about investigational drugs is considered confidential commercial information, it was not surprising that the FDA refused to confirm media reports and also denied a Freedom of Information Act request regarding the internal decision-making process that allowed the American missionaries to access the experimental drug. The FDA's refusal prompted the Goldwater Institute to file suit against the U.S. Department of Health and Human Services. The action is currently stayed while the court reviews the index of documents the FDA produced in response to the lawsuit.³⁴

In addition to the FDA's reluctance to disclose its involvement, MappBio never revealed its decision-making process in agreeing to make ZMapp available. What factors were influential in the company saying yes? It can take up to 6 months to produce a single dose of ZMapp, and MappBio only had a limited quantity of the drug available.³⁵ What criteria did the company use to determine who would get access? Did MappBio approve access based on: first come, first serve, the sickest, Americans first, those mostly likely to recover? In granting these immediate requests, what consideration, if any, did the company give to future patients? In other words, after the quantity of experimental drug was exhausted, what impact would that have on future clinical trials necessary for ultimate FDA approval? The company's silence left the public with a renewed interest in better understanding what influences drug companies' decision-making processes.

Social Media Campaigns

Patients are increasingly using social media to influence drug company use practices. Through Facebook, Twitter, YouTube, and other social media platforms, patients try to raise awareness for their cause, attract traditional media coverage, generate online petitions, and otherwise exert public pressure on drug companies to grant patient requests to use their experimental drugs for expanded access. The family of Josh Harding and Andrea Sloan launched two of the more notable social media campaigns.

In 2014, after the drug company Chimerix repeatedly refused 7-year-old Josh Hardy's expanded access requests, his family launched a social media campaign to pressure the company to provide access to the drug Brincidofovir. His mother posted "Please help us save our son" on her Facebook page and within hours the drug company was inundated with Facebook and Twitter requests to provide

the drug. Overnight, local and national media outlets picked up the story and the Hardy family was featured on CNN.³⁶ In the wake of the media coverage, the company reversed its previous denial and provided Josh the experimental treatment. It is important to note, however, that Chimerix did not approve the drug for expanded access. Rather, working with the FDA, Chimerix hastily approved a clinical trial and authorized the use of the drug in 20 patients. Having the experimental drug used in a clinical trial, as opposed to expanded access, allowed the company to use the data gathered from the patients as part of its drug approval application. It is the FDA's long-standing policy that it does not consider expanded access data when evaluating a drug's efficiency for marketing approval. The challenge facing the 55-person company was that it was heavily leveraged, had limited financial resources, and similar to MappBio, did not have enough of the drug to make it available for everyone seeking access and still have enough to use in clinical trials. According to the company, getting Brincidofovir successfully through clinical trials and approved by the FDA was the best way to protect the company and help future patients.³⁷

While the results are mixed, for patients and their families, social media campaigns are becoming a strategy of choice. Patients have launched social media expanded access campaigns against 13 pharmaceutical companies including household names, Bayer AG and Eli Lilly, mid-sized companies, and small start-ups such as CureTech Ltd.³⁸ Change.org, an online petition tool that hosts expanded access campaigns is one of the more frequently used sites for expanded access campaigns. Currently, the online platform has over 100 million users in 196 countries.³⁹

Andrea Sloan a 30-year-old attorney was diagnosed with ovarian cancer in 2006. After 7 years of standard therapy approaches including five surgeries, stem cell transplant, and two rounds of chemotherapy, she had exhausted all FDA-approved methods to battle her spreading cancer. As a last resort, her physician recommended an experimental PARP inhibitor being developed by Biomarín pharmaceuticals. Sloan immediately contacted the FDA and learned that she met all the requirements for expanded access and that her application would be quickly approved once Biomarín agreed to make the drug available.⁴⁰

Biomarín summarily refused to provide Sloan access to its drug. After repeated requests to understand the basis of the company's denial, Sloan launched a social media campaign to pressure Biomarín to have an open dialogue

³⁶ Cohen (2014).

³⁷ Flatten (2016).

³⁸ Mackey and Schoenfeld (2016).

³⁹ Mackey and Schoenfeld (2016).

⁴⁰ Flatten (2016).

³⁴ Kaye (2014).

³⁵ Kaye (2014).

about possible ways to provide her treatment without jeopardizing the company's drug approval efforts. Sloan also started a Change.org petition and received over 190,000 supporters. Her battle with Biomarin received national news coverage and attracted the attention of U.S. Representative McCaul and former House Speaker Newt Gingrich. Biomarin's refusal to provide information explaining its evaluation and subsequent denial of Sloan's request prompted Representative McCaul to author a white paper and draft the Andrea Sloan Cures Act (Sloan Act) in an effort to reform drug company practices related to patient access to experimental treatments. Provisions of the Sloan Act were included in the recently passed 21st Century Cures Act.

Notwithstanding public and political pressure, Biomarin's position remained unchanged. In October 2013, another company developing a similar experimental PARP inhibitor agreed to provide Sloan access on the condition that it name not be disclosed. Three months had passed since Sloan's initial expanded use request and during that time her condition worsened. While Sloan initially responded well to the experimental treatment, she developed pneumonia and died on January 1, 2014.

In response to these efforts, expanded access literature was quick to note that while social media campaigns helped Josh Hardy and Andrea Sloan, these types of practices can result in inequitable distribution of unapproved treatments. The literature highlights the reality that in these cases, the patients most capable of exploiting social relationships on- or off-line were the most likely to gain access.⁴¹ As a result, the debate continues to exist on whether or not social media should have any role at all in the access decision-making process.⁴² While social media campaigns appear to generate mixed results in influencing drug company decisions, patients using these actions have had positive results in influencing state and federal representatives to increase access to experimental drugs through legislation.

State Right to Try Legislation

Based on a 2014 model law drafted by the Goldwater Institute, Right to Try laws are designed to make it faster and easier for patients to obtain experimental treatments by overriding FDA and independent review board (IRB) restrictions.⁴³ Over 27 states allow patients to request drug companies to provide experimental treatment at the end of Phase I testing based on a physician's recommendation and attestation as to the inadequacy of an FDA-approved treatment option.⁴⁴ More than 30 states have laws that

include a provision that prevents medical boards from taking disciplinary action against physicians solely because they recommended the experimental drug.⁴⁵ Another standard provision in Right to Try legislation is that states provide pharmaceutical companies limited immunity from harmed caused by their unapproved drugs.⁴⁶ Other states including Oklahoma allow access to experimental treatments if patients do not live with 100 miles of a clinical trial or if they have not been accepted into a clinical trial within 1 week of applying.⁴⁷ Oregon is one of the few states that requires a patient to have less than 3 months to live as a condition before granting access to experimental treatments.⁴⁸

As of November 2016, 32 states have passed Right to Try laws and several more are considering similar legislation.⁴⁹ Under the Trump administration, the trend could continue. During the election campaign, then Indiana-governor and now Vice President Pence stated that he supports all state Right to Try laws.⁵⁰ More recently, Pence advocated for federal legislation that would provide terminally ill patients broader access to experimental drugs. Shortly thereafter in January 2017, U.S. Sen. Ron Johnson reintroduced the Trickett Wendler Right to Try Act. If passed, this federal counterpart to state Right to Try legislation would prevent the federal government from taking action to prohibit patient access to experimental drugs that have completed Phase I clinical testing.⁵¹

While generating an ethical debate and publicity, these laws have had little effect on drug companies' expanded access practices.⁵² This is because state and federal laws do not, and cannot, compel drug companies or insurers to provide and pay for experimental treatments.⁵³ Additionally, while unlikely outside of particularly egregious circumstances, it is possible for physicians who prescribe experimental drugs pursuant to the state regulations, violate federal law and could lose their Drug Enforcement license registration.^{54, 55} Given these structural limitations, no drug company has granted a patient access to experimental treatments pursuant to a Right to Try law. Further, on an

⁴¹ Caplan and Moch (2014).

⁴² Caplan and Moch (2014).

⁴³ Gaffney (2015).

⁴⁴ H.R. 1281 (2014).

⁴⁵ Zettler and Greely (2014).

⁴⁶ H.R. 1281 (2014).

⁴⁷ http://webserver1.lsb.state.ok.us/cf_pdf/2015-16%20ENR/hB/HB1074%20ENR.PDF.

⁴⁸ Tenth Amendment Center (2013). Right to Try. Retrieved from <http://tracking.tenthamendmentcenter.com/issues/right-to-try/>.

⁴⁹ Bateman-House (2016).

⁵⁰ Edney (2017).

⁵¹ S.2912 Trickett Wendler Right to Try Act (2016).

⁵² Zettler and Greely (2014).

⁵³ Zettler and Greely (2014).

⁵⁴ Darrow et al. (2015).

⁵⁵ Darrow et al. (2015).

industry level, both PhRMA and the Biotechnology Industry Organization (BIO) have expressed reservations about the laws and doubt their ability to increase the availability of new, safe, and effective medication for patients.⁵⁶

Finally, if challenged, it is expected that a court will find these state Right to Try laws unconstitutional based on the Supremacy Clause which grants federal law precedence over any conflicting state law.^{57, 58} Through expanded access regulations, the federal government has provided a pathway for individuals to gain access to experimental drugs. Accordingly, the FDA could challenge a competing state-approved process to access experimental drugs. Notwithstanding the questionable legal footing of Right to Try laws, they continue to garner the support of patient advocacy groups, legislators, and the media.⁵⁹

The most recent development relating to expanded access and the law was the passing of the 21st Century Cures Act. Section 3032 of the Act requires companies that make investigational drugs that address a serious or life-threatening disease to make their expanded access decision-making policies publically available. The companies must include contact information for investigational drug requests, the procedures for obtaining these drugs, the general criteria for evaluating expanded access requests, and a link or reference to the clinical trial record. The Cures Act contains the caveat that posting of policies by drug companies is not a guarantee of access to any specific experimental by any individual patient. A company may also revise its policy at any time. While the Cures Act includes penalties for non-compliance it is unclear whether they apply to expanded access. As of March 2017, the new mandates have increased the number of drug companies that provide information related to expanded access on their Web site; however, many of the policies listed on the Web sites are still unclear or have yet to be updated. Since the passage of the Cure Act, only one out of the top ten pharmaceutical companies that we analyzed has notified the public of their updated policies, GlaxoSmithKlein. Without proper buy-in from drug companies, to update and publish their expanded access policies, the potential barriers that patients and their referring physicians will face while attempting to obtain expanded access drugs remains uncertain.

Patient social media campaigns, increased television coverage, and the recently enacted Cures Act demand drug companies create and make publicly available their

evaluative and decision-making processes that up until now they have been reluctant to disclose. The following section examines potential reasons why.

Drug Companies' Complex Role in Expanded Access

Practical Considerations

The intricacies inherent in the drug development and approval process present a host of legal, ethical, logistical, and financial challenges to drug companies considering whether to make their experimental drugs available to patients. Drug companies have expressed concern that providing access to experimental drugs could undermine new drug development.⁶⁰ Historically, there has been a shortage of available and qualified subjects willing to participate in drug trials and currently, less than five percent of cancer patients enroll in U.S. clinical trials.⁶¹ If patients can access experimental drugs from their doctors locally, then there is less incentive to travel to sites to participate in clinical trials.⁶² This increased availability could decrease interest in participation and thus enrollment in a clinical trial.⁶³ Drug companies are concerned that decreased enrollment would compromise the ability to collect sufficient data on safety and efficacy and consequently delay drug approval by the FDA.⁶⁴

In the extreme, companies raised the concern that expanded access could encourage clinical trial patients to try and “game” the system in an effort to maximize access to experimental treatments.⁶⁵ While the majority of Phase III clinical trials are placebo-controlled, double-blinded studies, it is possible for patients to determine whether they have been randomized to receive placebo, especially if they do not experience the expected side effects.⁶⁶ Identifying one's randomization group and voluntarily withdrawing from a trial in an attempt to obtain the experimental drug via expanded access has occurred, as seen in a 2014 case involving a woman with cancer.⁶⁷ After withdrawing from the trial, the company denied her request, thus failing to meet her interests and failing to achieve their goals of increased participation in clinical trials.

⁶⁰ Darrow et al. (2015).

⁶¹ Cameron (2014).

⁶² Darrow et al. (2015).

⁶³ Walker et al. (2014).

⁶⁴ Walker et al. (2014) and Okie (2006).

⁶⁵ Proposed new drug (1983).

⁶⁶ Docker Marcus (2014).

⁶⁷ McDiarmid (2014).

⁵⁶ Zettler and Greely (2014).

⁵⁷ Mutual Pharmaceutical v. Bartlett (2013).

⁵⁸ Food and Drug Admin. v. Brown & Williamson Tobacco Corp. (2000).

⁵⁹ Zettler and Greely (2014).

Another concern expressed by the drug companies is the potential negative effect of expanded access on their drug approval efforts. While adverse effects rarely affect drug development,⁶⁸ companies must report all pre-approval adverse events involving patients who receive expanded access drugs.⁶⁹ The FDA considers that data, as well as data derived from clinical trials when evaluating the drug's safety.⁷⁰ Patients requesting expanded access are often sicker than patients participating in clinical trials, and as a result, companies fear that complications that may arise with terminally ill patients could negatively affect the drug's FDA evaluation and approval. Further, companies note that because these unapproved drugs are administered outside of a controlled and regulated clinical trial, outcomes (either beneficial or adverse) could be misleading.⁷¹ Interestingly, the FDA's practices echo this point. While the FDA reviews expanded access data in evaluating safety, the FDA will not accept this data as evidence of a drug's efficacy and states, "the FDA recognize[s] that such data may not be collected in a systemized fashion and, therefore, may not be useful".⁷²

Drug companies also note that shareholder claims could result if an expanded access use negatively impacts the company. For example, if clinical trials are postponed or terminated based on expanded access adverse events. Expanded access outcomes could also pose a risk of shareholder litigation if they are not reported carefully. In *Glaser v. Enzo Biochem Inc.*, shareholders brought suit against company executives alleging that they made fraudulent statements that Phase II and Phase III would be fast-tracked based on the drug's expanded access experience. While the court ultimately rejected this claim, drug companies are aware that claims such as this may be alleged.⁷³

The manufacturing and production costs of bringing a new drug to market are substantial. As a result, the FDA now permits drug companies to charge patients or their insurers for expanded access treatments.⁷⁴ However, companies have discovered that this is a double-edged sword:

Charging direct costs...can lead to adverse publicity because these costs will be far less than the price of a drug when it is ultimately approved by the FDA, a price that sometimes exceeds \$1,000 per pill or

\$200,000 per patient per year. [As a result,] manufacturers...guard cost information carefully, even if it means forgoing the modest revenue that might be obtained through this [regulatory] pathway.⁷⁵

Further, because Medicare, Medicaid, and private insurers do not cover experimental Phase I treatments, patients may pressure companies to waive the cost of the drug. In addition, if the company finds it necessary to track and monitor these drugs' expanded access, the additional costs above research and development in the standard clinical trials may force the manufacturer to raise retail prices to a point that access to the general public post-approval is not feasible.⁷⁶

Drug Companies' Expanded Access Policies & Practices

The Cures Act contains four different requirements for transparency of expanded access policies. Given the critical role drug companies play in a patient's access to unapproved drugs, they are facing mounting requirements to make their expanded access policies readily available. Avalere Health, a private firm based out of Washington D.C., completed a query using the top 100 pharmaceutical and biotechnology firms ranked according to market capitalization. Their research found that only 19% of pharmaceutical and biotechnology companies publically post their compassionate use and expanded access policies on their Web sites.⁷⁷ Additionally, the same research found that 52% of large companies (> \$10B market cap), 14% of medium companies (\$1.5B-\$10B), and 4% of small companies (< \$1.5B) contained information on their website about expanded access.⁷⁸ To complete a more in-depth assessment of the quality of drug companies' publically available expanded content, this article explored the websites of the ten largest pharmaceutical companies worldwide, based on 2016 revenue. Each of the ten companies assessed (GlaxoSmithKlein, AstraZeneca, Gilead, Sanofi, Merck, Roche, Pfizer, Novartis, Bayer, and Johnson and Johnson) were subject to a basic online query and each produced a company page addressing expanded access requests (Fig. 4). The quality and availability of information on a drug company's page was then assessed, specifically looking at six metrics: the company's stance on an unapproved drug's quality/efficacy, patient eligibility to submit a request, requirement for a physician and larger

⁶⁸ Jarow et al. (2016).

⁶⁹ Food and Drug Administration, HHS (2009).

⁷⁰ Darrow et al. (2015).

⁷¹ Food and Drug Administration, HHS (2009).

⁷² Food and Drug Administration, HHS (2009).

⁷³ In *Glaser v. Enzo Biochem Inc.*, 303 F. Supp. 2d 724 (E.D. Va. 2003),.

⁷⁴ Food and Drug Administration, HHS (2009).

⁷⁵ Darrow et al. (2015).

⁷⁶ Ochs (2009).

⁷⁷ Huneycutt et al. (2016).

⁷⁸ Huneycutt et al. (2016).

hospital system (mainly the IRB) to be involved, potential impact on request decision based on a conflict of interest with an ongoing clinical trial, how the drug would be distributed if limited in quantity, and how to initiate an expanded access request. As can be seen in the table below, all of the companies assessed provide policies that simply echo the FDA's expanded access requirements. The ten pharmaceutical companies looked at all require that perspective recipients must (1) have a serious or life-threatening disease; (2) no other available treatment options, and (3) sufficient evidence must exist to make a basic safety efficacy determination. However, this is an inadequate approach because there is a gap between expanded access regulations and Cures Act provisions.

The Cures Act requires companies to disclose general criteria used to evaluate expanded access requests. FDA regulations establish the minimum patient eligibility requirements, and through subsequent industry guidance, the agency describes its role, as well as a physician's role, in evaluating patient requests. Perhaps because the FDA cannot compel a company to make its drug available, industry guidance for addressing drug company criteria to evaluate requests is scant in several areas. Shire, a smaller pharmaceutical company outside of the larger companies, and Janssen (a division of Johnson and Johnson) were selected as examples to illustrate some of the expanded access approaches that substantively fill the gap between FDA regulations and the Cures Act requirements. Both Shire and Janssen provide patients with Web sites that address patient questions about the evaluation process, as well as treat them in a fair, transparent, and timely manner.

Shire

Shire's expanded access policies are noteworthy in their attempt to transform the FDA's benefit–risk analysis requirements into real-world evaluation criteria and business practices that insulate the company from future litigation. Drug companies must face the reality of potential liability associated with patient harm and the hindrance of future product development issues as a result of adopting the FDA risk benefit requirement as is. Naturally, drug companies have likely found it difficult to balance their interests in providing unapproved and potentially dangerous medications to those in need while simultaneously protecting the drug's ability for future trials, approval, marketing and profitability.

The FDA expanded access evidentiary standard allows the patients to access the experimental drug “in the absence of any clinical data to support [that] the use may carry substantial risk”.⁷⁹ Rather than adopting the FDA's risk–

benefit evidentiary threshold, Shire took a different approach. In particular, Shire's practices note: “For patients, expanded access may bring potential safety risks or a false sense that the medicine will provide benefit; for the clinical development program, it can delay or jeopardize the approval of a new medicine sought by many”.⁸⁰ Shire's practices further develop this discussion by imposing criteria on the minimum safety profile of the experimental drug. As previously noted, FDA regulations permit making an experimental drug available to individual patients without any clinical data to support the drug's safety and effectiveness.⁸¹ Departing from this approach, Shire requires that sufficient safety and efficiency data exist to conduct a benefit–risk analysis. According to Shire's policies, this cannot occur prior to the end of Phase II studies. Even if these conditions are met, Shire does not guarantee that the expanded access program will be available. Further, even if such a program is available, Shire works to manage expectations and will not guarantee that the experimental drug will be available to a particular patient.⁸²

Shire's policy also addresses, albeit incompletely, the FDA's provision regarding expanded access procedures in times of scarcity. The FDA acknowledges the need for a fair and equitable way to allocate experimental drugs when demand exceeds supply. However, expanded access protocols do not contain any regulatory provisions establishing what that process should resemble.⁸³ Shire will only make its experimental drugs available if there is an adequate supply of the drug for both the expanded access request and the ongoing clinical trials.^{84, 85}

Finally, Shire's policies respond to patient concerns regarding procedural transparency that are not sufficiently addressed by current regulations or industry guidance. Shire differentiates itself from other pharmaceutical companies by publically stating that requests will be evaluated in a fair, unbiased manner and acknowledged within three business days. Shire's practices also appear to provide more informed consent considerations than required by the FDA. Expanded access regulations require patients to agree to informed consent disclosures designed for clinical trials. However, expanded access is a distinct process from a clinical trial with different aims that involve neither research nor investigation. As such, tailored disclosures

⁸⁰ “Shire Policies: Expanded access.” *Shire Policies: Expanded access*. N.p., n.d. Web. 13 June 2016..

⁸¹ “Shire Policies: Expanded access.” *Shire Policies: Expanded access*. N.p., n.d. Web. 13 June 2016..

⁸² “Shire Policies: Expanded access.” *Shire Policies: Expanded access*. N.p., n.d. Web. 13 June 2016..

⁸³ Food and Drug Administration, HHS (2009).

⁸⁴ Shire Policies: no access (2016).

⁸⁵ Genentech: Investigational Medicines (2016).

⁷⁹ Food and Drug Administration, HHS (2009).

that address the specific risks and benefits unique to expanded access are a necessary part of a complete and thorough framework, which drug companies can use. While the entire Shire process once a patient is approved is not clear, accepted expanded access patients must agree to Shire-defined informed consent and safety and monitoring requirements in addition to FDA informed consent provisions.⁸⁶ No details on Shire's safety and monitoring requirements are publically provided; however, it is clear that Shire's standard patient workflow regarding the informed consent provisions and the safety and monitoring requirements exceed what is currently required by the FDA.

Janssen

In early 2015, Janssen Pharmaceutical Companies (Janssen) of Johnson & Johnson partnered with the Division of Medical Ethics at NYU to develop a review process for expanded access requests.⁸⁷ The result was the creation of the Compassionate Use Advisory Committee (CompAC), an independent ten-person committee consisting of physicians, bioethicists, patients, and patient advocates from five countries. To ensure fair, unbiased, and even-handed decisions that promote patient and physician trust, the CompAC created a multi-part evaluation process.⁸⁸ This approach was piloted with Daratumumab, a drug in late-stage clinical trial development that had shown promise in treating patients with multiple myeloma refractory.⁸⁹ Due to manufacturing constraints and rapidly progressing clinical trials, only a small amount of the drug was available for expanded access. The CompAC set about to create a publicly available set of processes used to evaluate patient's expanded access requests.⁹⁰

According to the CompAC-established protocols, patients that are ineligible for clinical trials are referred to the committee for independent expanded access evaluation. As a legal matter, Janssen makes the final determination regarding whether or not to provide the drug; however, Janssen relies on and follows the CompAC recommendations in 97% of cases.⁹¹

The Janssen submission process requires that all requests be made anonymous to prevent possible bias based on income, nationality, sex, race, or celebrity status. In reviewing requests, the committee consults internal and

external subject matter experts to provide scientific and technical insights to assist in evaluation. Patients and physicians are notified of the committee's response within five business days of submission. The CompAC process includes an appeals process that allows physicians to submit additional patient information. In the cases where the CompAC approves the request, the process provides the drugs at no cost to the patient.⁹²

From July 1 through December 31, 2015, Janssen received 160 requests for Daratumumab. Seventy-six of those requests were referred to the CompAC, who went on to recommended expanded access for 60 of them; Janssen approved an additional two requests.⁹³ Since the running of the pilot project, the FDA has approved the drug for distribution to the public. The CompAC is currently in the process of examining the impact of its review process and the suitability of other drugs. According to the CompAC, the major lessons learned from the Daratumumab pilot are that both fairness and justice are critical components in evaluating patient expanded access requests.⁹⁴

The CompAC is the first independently administered and publically available process that evaluates expanded access requests. It created a standardized review process that addresses some of the expanded access regulatory deficiencies and patient and physician concerns. The CompAC framework further addresses concerns surrounding patient fairness by including due process protections. For example, the process affords applicants the right to be heard, receive an expeditious response to their request, and file an appeal process should their physician disagree with the committee's determination.⁹⁵ The CompAC approach also notes that it strives to incorporate justice principles into its evaluative process. According to CompAC, primary considerations addressing justice are the desire to not harm patients, the requirement to exhaust all approved treatment options, and the necessity to evaluate the scientific likelihood of an effective response.⁹⁶ Unlike the other novel aspects of the CompAC's criteria, as applied, these considerations appear to do little more than restate the FDA expanded access benefit-risk assessment.

Biotechnology Industry Organization and PhRMA Guidance

Other guidance offered by the industry comes from BIO and PhRMA. Rather than providing concrete recommendations like those included in the CompAC process, BIO's

⁸⁶ "Shire Policies: Expanded access." *Shire Policies: Expanded access*. N.p., n.d. Web. 13 June 2016..

⁸⁷ Caplan and Ray (2016).

⁸⁸ Caplan and Ray (2016).

⁸⁹ Caplan and Ray (2016).

⁹⁰ Caplan and Ray (2016).

⁹¹ Caplan and Ray (2016).

⁹² Caplan and Ray (2016).

⁹³ Caplan and Ray (2016).

⁹⁴ Caplan and Ray (2016).

⁹⁵ Caplan and Ray (2016).

⁹⁶ Caplan and Ray (2016).

approach identifies issues that companies should consider as they develop their expanded access policies. Similar to the concerns raised by the CompAC, BIO emphasizes the need to develop fair and equitable inclusion and exclusion criteria to evaluate patient requests. When crafting equity requirements, BIO encourages companies to consider the severity of the disease, the physician's assessment of the benefit–risk ratio, and the number of doses available.⁹⁷ The board also stresses that a company's expanded access policies must contain a mechanism to level the playing field. In other words, the fact that patients may hire counsel, rally support through social media, or possess extensive knowledge about the product being developed does not mean that they are more deserving than others.⁹⁸

Once created, BIO recommends that companies make their expanded access criteria publically available and easily accessible. While noble in its intent, the challenge for many companies rests in how to transform this guidance into practice.

In June 2015, PhRMA released unanimously approved voluntary principles for biopharmaceutical companies considering participation in expanded access programs. In large part, the principles mirror FDA expanded access requirements. Consistent with the Cures Act requirements, the PhRMA principles also recommend establishing telephone or Internet information resources to facilitate communication between companies and patients' physicians about expanded access programs.

Recommended Framework

In creating a framework for drug company expanded access procedures, we began by focusing on the intent of the Cures Act's expanded access requirements. In particular, we noted the Congressional desire to address, through federal legislation, patient and physician frustration regarding the lack of transparency when trying to navigate drug companies' expanded access practices. From our analysis of existing practices, PhRMA and several companies have expanded access policies that restate FDA regulations. As previously stated, there are gaps between FDA and the Cures Act expanded access requirements. The proposed framework provides drug companies evaluative approaches designed to fill that void.

In addition to these legal and regulatory considerations, the recommended framework addresses a deeper issue in the expanded access debate. Namely, how to create company procedures that properly acknowledge and resolve the tension between a terminally or seriously ill patient's desire

to access experimental drugs and a company's desire to safeguard its drug approval processes and profitability. It is our contention that without established criteria to evaluate these competing concerns, companies may reflexively reject patient requests without adequate consideration. The Cures Act can compel drug company disclosure, but it cannot compel company participation in the expanded access process. The goal of the framework is to provide an approach that can increase drug company participation by addressing systemic tensions.

In reviewing existing policies, companies commonly referred to the need to ensure their processes are fair. Similarly, the ethical principles of fairness and justice are often referenced in expanded access literature as necessary underpinnings in addressing patient access to experimental drugs.⁹⁹ Building on that foundation, the recommended framework offers companies who are willing to say yes to making their drugs available, a practical, transparent, fair and just approach for evaluating and processing patient requests. While the Cures Act requires increased disclosures from drug companies, there are areas where increased transparency is needed to insure fairness and justice. The suggested framework includes such provisions (Fig. 3). The framework incorporates and enhances aspects of the CompAC's standardized submission and due process processes. From this platform, other procedural elements necessary to ensure transparency and fairness in drug companies' review of patient expanded access requests include: providing patients a single point of the contact and the ability to track their request as it moves through a company's expanded access evaluation. A draft version of the Cure Act required companies to provide written notice of the denial within five days after rendering the decision. To promote transparency and procedural fairness, companies should provide a detailed written explanation when a request is denied. Further, patients should be given the right to appeal denials. A possible approach could include an appeal before a non-binding third party such as an independent, multidisciplinary body or a regulatory agency like the FDA.

The framework also contains measures to promote fairness through increasing public awareness of expanded access. Company expanded access policies should be easy use to find and consistently identified. For example, the policy should be contained in a pulldown menu located on the company's home page. From our analysis, policies were identified as compassionate use, expanded access, and pre-approval access. To increase patients' ability to search and locate experimental drug information, companies should adopt the expanded access terminology used in FDA regulations and the Cures Act.

⁹⁷ "Expanded Access Programs: Points to Consider - BIO." (2016).

⁹⁸ "Expanded Access Programs: Points to Consider - BIO." (2016).

⁹⁹ Raus (2016).

Fig. 1 FDA individual expanded access criteria

FDA Individual Expanded Access Requirements (21 C.F.R. 312.310)
Patients has a serious or immediately life-threatening disease or condition
No comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition exists.
The potential patient benefit justifies the potential risks of the treatment, and those risks are not unreasonable in the context of the disease or condition being treated.
The expanded use of the investigational drug for the requested treatment will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the product.

Fig. 2 21st century cures act requirements

21 st Century Cures Act Requirements (Pub. L. No. 114-255, 130 Stat. 1033 (2016))
Contact information for the manufacturer or distributor;
The procedure for making requests under the policy;
The general criteria the manufacturer or distributor will use to evaluate and respond to requests including the length of time the manufacturer or distributor anticipates will be necessary to acknowledge receipt of requests
A hyperlink or other reference to the clinical trial record containing information about the expanded access for such drug

Fig. 3 Proposed framework for drug company expanded access policies

Proposed Drug Company Expanded Access	
Procedural Guidelines Designed to Promote Fairness and Transparency	
<ul style="list-style-type: none"> • Single point of contact • Online tracking of request • Standard anonymized submission request • 5-day response time • Clear specific criteria for evaluating and approving requests 	<ul style="list-style-type: none"> • Appeal process before an independent 3rd party • Detailed written explanation of denial • Expanded access policy easily accessible through drop menu on company’s home page
Substantive Guidelines to Promote Justice	
<ul style="list-style-type: none"> • Specifically tailored informed consent requirements • Sufficient preclinical data exists to evaluate the experiment drug’s safety and efficacy to avoid exposing patient to unnecessary harm (minimum requirement that expanded access drugs complete Phase 2B clinical studies) • Statement to patients explaining company’s primary responsibility is to develop and 	<ul style="list-style-type: none"> obtain full marketing approval for its drugs. This goal can prevent the granting of expanded access requests due to limited drug quantities, the priority of on-going clinical trials or other manufacturing constraints.

Company websites should maintain a database of all expanded access eligible drugs as well as a link to the company’s eligibility criteria. Further, companies should present this material in a format that can be easily understood by patients. Critics maintain that certain diseases, conditions, and populations, most notably women and minorities, have been underserved by expanded access programs.¹⁰⁰ To the extent possible, company frameworks should include contacts at a variety of government and private organizations that can provide resources and help underserved patients navigate through the expanded access process, an example being, the FDA’s Office of Special Health Issues. Increasing public awareness and access to this information will aid in the disparate knowledge among patients regarding possible treatment options. These

measures will also allow companies to better frame their interaction with patients requesting access to experimental treatment. In addition, similar to Janssen’s approach, company sites should include videos explaining their expanded access policies and procedures.

Outside of these procedural and administrative recommendations, there are regulatory deficiencies that companies should address in their expanded access frameworks. In concert with PhRMA and patient advocacy groups, companies need to create standardized informed consent disclosures that are specifically designed to address the vulnerabilities of patients with life-threatening or terminal diseases. This need is punctuated by the low evidentiary risk–benefit standard for providing access to expanded access drugs. At a minimum, informed disclosures should include where drug is in the clinical trial process and the likelihood that some of the drugs made available through

¹⁰⁰ Food and Drug Administration, HHS (2009).

An Overview of Expanded access (EU) Policies and Requirements for Leading Pharmaceutical Companies

Safety/Efficacy	Patient Eligibility	Physician/ Hospital	Impact on Continuing Clinical Trials	Quantity of Available Medicine	Request Response
JANSSEN/JOHNSON & JOHNSON (USA)					
https://www.jnj.com/media-center/press-releases/compassionate-use-backgrounder					
Risk of experimental treatment is reasonable in light of potential benefit. Risk is not unreasonable in the context of condition/disease being treated.	No other comparable or satisfactory treatment option available.		CU will not interfere with the initiation, conduct, or completion of clinical investigations and could support marketing and approval of expanded access.		Physician initiated with anonymized patient information. Janssen responds within 5 business days and permits appeals.
NOVARTIS (Switzerland)					
https://www.novartis.com/our-work/research-development/managed-access-programs					
Potential benefit of treatment use outweighs the potential risk in the context of the disease or the condition. Must be confirmed by treating physician.	Patient has no treatment options because standard of care (SoC) is ineffective, they have exhausted all of their options.		Patient is not eligible to enroll in a clinical trial. Provision will not interfere with ongoing clinical trials or overall development program.		Physician initiated.
PFIZER (USA)					
http://www.pfizer.com/research/compassionate_use					
Sufficient evidence supporting that the investigational product will have an acceptable safety profile.	Unsuccessful standard of care treatment. No alternative treatment is available or exists to diagnose, treat, or monitor the disease.	Agrees in writing to comply with country specific legal and regulatory requirements and Pfizer medical criteria, IP, safety reporting, and drug use/supply requirements.			Physician initiated. Requests from patients and non-healthcare are not accepted. Pfizer responds within 5 business days.
GENETECH/ROCHE (Switzerland)					
http://www.roche.com/dam/jcr:035f3847-505e-484c-b5f6-f666790791de/en/25_Position%20on%20Pre%20Approval%20Access%20on%20Investigational%20Medicinal%20Products_reviewed_9_2016.pdf					
Potential patient benefit outweighs the potential risks including the disease outcome itself. Sufficient clinical data must exist to identify dosing.	Must not qualify for any ongoing trial and must have exhausted all SoC therapies. Must not have any underlying medical conditions that have not been sufficiently characterized/studied.	The FDA and administering hospital's IRB must review and approve use of the medicine.	CU does not interfere with the completion of clinical trials that can support FDA approval or otherwise compromise the potential development of investigational medicine.	Must have adequate supply of the experimental treatment.	Physician initiated. Requests from patients are not accepted.
BAYER (Germany)					
http://pharma.bayer.com/de/engagement-und-verantwortung/ethik-und-transparenz/ethik-in-fe/compassionate-use/					
Product must have shown a favorable benefit-risk profile in Phase III clinical trials.	Suffering from a significantly debilitating or life-threatening condition that cannot be satisfactorily treated with an approved medicinal product. Patient has received the appropriate SoC without success and no alternative drug is available. Patient meets the criteria of participation but is not eligible for an ongoing clinical trial.		Patient will be screened to check whether they are suitable for participation in a clinical trial.		
MERCK & CO. (USA)					
http://www.merck.com/about/views-and-positions/access-to-medicines/home.html					
Sufficient evidence to expect that the medicine will have an acceptable safety profile for the specific patient population so that the patients are not exposed to unreasonable risks. Potential benefit to health outweighs the risk of harm.	Disease is similar in type and stage to the indications for which the medicine is currently being studied and for which there is sufficient evidence of efficacy to expect that the individual may derive clinically many meaningful benefit.		Participation in clinical trials should be the primary route for obtaining investigational medications.	Adequate supply of the investigational medicine exists to perform necessary clinical trials as well as sustainably and equitably provide access to other patients who have no alternative treatment options.	Physician initiated.
SANOFI (France)					
http://en.sanofi.com/Innovation/clinical-trials-and-results/access-to-investigational-products/access-to-investigational-products.aspx					
A favorable benefit/risk ratio for the investigational product based on the most current human safety and efficacy data must be achieved.	Evaluated on a case-by-case basis which considers the patient's condition when they have no viable SoC options. Medical criteria that allows for CU must be met.	Treating physician must obtain IRB approval.	CU does not interfere with any ongoing clinical trials at Sanofi.	Must have adequate supply of the investigational product.	Physician initiated.

Fig. 4 Overview of expanded access requirements for lead drug companies

GLAXOSMITHKLEIN (UK)					
http://www.gsk.com/en-gb/healthcare-professionals/compassionate-use-expanded-access/					
Sufficient evidence to believe that the benefit to the patient justifies the risk must exist. Use will be in a country where GSK intends to seek regulatory approval.	Illness is life threatening or seriously debilitating, there are no satisfactory alternative treatments.		Possibility of CU compromising any related clinical trial or regulatory pathway will be a key consideration.		Physician initiated.
ASTRAZENECA (USA)					
https://www.astrazeneca.com/content/dam/az/PDF/2016/AstraZeneca_Policy_on_Early_Access_to_Investigational_Medicines.pdf					
Investigational medicine must be the subject of an active clinical development program and is not approved in any indication in the country concerned. There must be sufficient clinical data available to anticipate that any potential benefits from treatment are likely to outweigh any associated patient risks.	Patient is suffering from a serious or life-threatening disease and has exhausted other therapeutic options. Patient's medical status is deemed appropriate to receive CU medicine and patient will receive treatment in the country/jurisdiction where AstraZeneca plans to seek marketing approval for drug.		Request does not impede or compromise the clinical development or regulatory approval of medicine under investigation. Patient is not eligible to enroll in a clinical study for medically valid reasons and is otherwise unable to participate in an AstraZeneca clinical trial.	An adequate supply of the investigational medicine exists to perform necessary clinical studies as well as to provide Early Access to patients who do not have alternative treatment options.	Physician initiated.
GILEAD (USA)					
http://www.gilead.com/research/expanded-access					
A strong biological rationale or clinical data exists to support the belief that the potential benefits of the investigational drug outweigh the potential risks.	Patient's physician has determined that the investigational product is in the patient's best interests. No therapeutic alternative is available. Patient has a serious/life-threatening condition.		Patient is not eligible to participate in a clinical trial or similar sponsored access program.		Physician initiated. Requested medicine, physician's intended treatment plan, therapeutic indication, expected duration and rationale for alternative therapy must be included. Response typically sent within 30 days of request.
SHIRE (Ireland)					
https://www.shire.com/who-we-are/how-we-operate/policies-and-positions/compassionate-use					
Sufficient preliminary data to assess risk/benefit ratio and dosing. Cannot occur before "Phase 2b" in studies.	Must not qualify for any ongoing trial.	Treating physician and Shire's Head of Clinical Development both reasonably expect benefit from the treatment.	Patient is not eligible for a Shire-sponsored study on the therapy or is limited by geographic constraints.		Physician initiated request, unsolicited by Shire or any other individual or organization. Shire responds within 3 business days.

Fig. 4 continued

expanded access will ultimately be shown to have no benefit and could in fact cause the patient harm.¹⁰¹

While disclosures should appropriately alert patients to the inherent risks of taking experimental drugs, company policies must be careful not to condition access on a patient waiver of liability. The FDA regulation states, "No informed consent, whether oral or written, may include any exculpatory language through which the subject...is made to waive any of the subject's legal rights or, releases...the investigator, the sponsor, the institution, or its agents from liability for negligence."¹⁰² Accordingly, state Right to Try laws premised on a patient's waiver of liability resulting from treatment with the experimental drug is illegal.

Companies should take particular care in explaining their risk-benefit evaluation procedures. Expanded access regulations permit access to experimental drugs even "in the absence of any clinical data to support the use may

carry substantial risk."¹⁰³ Companies may be uncomfortable adopting this standard. Accordingly, policies need to alert patients of the point in the drug's development when an appropriate risk-benefit analysis can be made. Borrowing from Shire's policy, requiring drugs to have completed Phase II or equivalent level studies is an appropriate benchmark. At this point, the drug has completed sufficient preliminary safety and efficacy evaluation to determine the potential risk to the patient. It is only with this information that risks and benefits can be assessed and informed consent can be given, understood, and provided. The CompAC pilot avoided directly addressing this issue by selecting a drug in the late stage of development, an approach suitable when the company invites the public to request access. However, in the vast majority of cases, patients seek access at earlier stages in a drug's development. In these instances, the request is not in response to a company overture, but in response to an immediate and dire need for an experimental drug (Figs. 1, 2, 3, 4).

¹⁰¹ Food and Drug Administration, HHS (2009).

¹⁰² Food and Drug Administration, HHS (2009).

¹⁰³ Food and Drug Administration, HHS (2009).

Finally, it is essential that access to experimental drugs does not compromise the integrity of the drug approval process. Company expanded access frameworks need to educate patients and make clear the constraints on the availability of experimental treatments. In particular, experimental drugs will not be available if pre-approval access will jeopardize ongoing clinical trials. For example, when a request is made before the enrollment for a clinical trial is completed or in cases of orphan diseases where there is a smaller population of patients to draw from for clinical trials, pre-approval access compromises patient enrollment in clinical trials and should be denied.¹⁰⁴ In addition, as noted previously, the FDA does not consider expanded access efficacy information for marketing approval. Accordingly, if limited drug supplies are exhausted through individual expanded access requests, the clinical trial process is delayed and the public's access to the drug is jeopardized. By providing the public with clearly defined procedures that address these possibilities, companies increase transparency and are able to educate patients as to the balance that must be struck between individual access and public access. Ultimately, expanded access frameworks need to emphasize to individual patients as well as the general public that the safest form of access to a drug is only after full marketing approval.

Conclusion

Over the last decade, a confluence of factors has elevated the expanded access debate to new heights. With FDA approvals of patient requests virtually guaranteed, drug companies have become the de facto gatekeepers of access to experimental drugs. As a result, patients, physicians, and state and federal lawmakers are increasingly focused on drug companies and their expanded access decision-making processes. Interactions that at one time were private conversations between a patient and the drug company are now played out across social media, television, and the courts. The need to have well-crafted and publically available expanded access criteria to frame those conversations is essential. The challenge is for companies to construct a framework that appropriately balances the desires of individuals and gaining the requisite approvals ensure access not just for one person but for society.

References

- Abigail Alliance v. von Eschenbach, 495 F. 3d. 695 (D.C. Cir. 2007)
- Adebamowo, C., Bah-Sow, O., Binka, F., Bruzzone, R., Caplan, A., Delfraissy, J. F., et al. (2014). Randomised controlled trials for Ebola: practical and ethical issues. *Lancet*, 384(9952), 1423.
- Bateman-House, A. (2016). Right-to-try laws could curtail the development of innovative new therapies. Retrieved from <https://www.statnews.com/2016/11/09/right-try-laws/>.
- Brower, V. (2014). Food and Drug Administration responds to pressure for expanded drug access. *Journal of the National Cancer Institute*, 106(6), 171.
- Buhles, W. C. (2011). Compassionate use: a story of ethics and science in the development of a new drug. *Perspectives in Biology and Medicine*, 54(3), 304–315.
- Cameron, S. (2014). Trials for new Cancer Treatments Reach Only a Tiny Fraction of Patients. Healthline. <http://www.healthline.com/health/cancer/trials-for-new-treatments-reach-few-patients>.
- Caplan, A., & Moch, K. (2014). Rescue me: The challenge of compassionate use in the social media era. *Health Affairs Blog*. <http://healthaffairs.org/blog/2014/08/27/rescue-me-the-challenge-of-compassionate-use-in-the-social-media-era/>.
- Caplan, A. L., & Ray, A. (2016). The ethical challenges of expanded access. *JAMA*, 315(10), 979–980. doi:10.1001/jama.2016.0416.
- Cohen, E. (2014). Company denies drug to dying child. Retrieved from <http://www.cnn.com/2014/03/10/health/cohen-josh>.
- Darrow, J. J., et al. (2015). Practical, legal, and ethical issues in expanded access to investigational drugs. *New England Journal of Medicine*, 372(3), 279–286.
- Docker Marcus, A. (2014). Researchers fret as social media lift veil on drug trials. *Wall Street Journal*. July 29, 2014 <http://www.wsj.com/articles/researchers-fret-as-social-media-lift-veil-on-drug-trials-1406687404>.
- Edney, A. (2017). Dying Patients Have Pence's Backing on 'Right to Try' Policy. Bloomberg. Retrieved from <https://www.bloomberg.com/news/articles/2017-02-08/pence-piles-on-drugmakers-with-push-for-right-to-try-regulation>.
- Eichler, H. G., et al. (2013). The risks of risk aversion in drug regulation. *Nature reviews Drug discovery*, 12(12), 907–916.
- Expanded Access Programs: Points to Consider - BIO. (2016). N.p., n.d. Web. 13 June 2016.
- Flatten, M. (2016). Dead on Arrival: Federal "Compassionate Use" Leaves Little Hope for Dying Patients (Rep.). Goldwater Institute.
- Food and Drug Admin. v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 133-34 (2000)
- Food and Drug Administration, HHS. (2009). Expanded access to investigational drugs for treatment use. Final rule. *Federal Register*, 74(155), 40900.
- Gaffney, A. (2015). Right to Try Legislative Tracker. <http://www.raps.org/Regulatory-Foexpandedaccess/News/Databases/2015/06/24/21133/Right-to-Try-Legislation-Tracker/>.
- Genentech: Investigational Medicines. (2016). *Genentech: Investigational Medicines*. N.p., n.d. Web. 13 June 2016.
- H.R. 1281, Gen. Assemb., Reg. Sess. (Colo. 2014); H.R. 1685, Gen. Assemb., Reg. Sess. (Mo. 2014); 46. H.R. 891, Gen. Assemb., Reg. Sess. (La. 2014).
- Huneycutt, B., Mermelstein, N., & Woollett, G. (2016). *Current state of transparency of manufacturer's compassionate use policies (rep.)*. Washington, DC: Avalere Health.
- Jarow, J. P., Lemery, S., Bugin, K., Khozin, S., & Moscicki, R. (2016). Expanded access of investigational drugs: the experience of the center of drug evaluation and research over a 10-year period. *Therapeutic Innovation & Regulatory Science*, 50(6), 705–709.
- Kaye, R. (2014). How the Ebola drug ZMapp is made. Retrieved from <http://khon2.com/2014/10/06/how-the-ebola-drug-zmapp-is-made/>.
- Kim, T., Lurie, P., & Pazdur, R. (2015). US Food and Drug Administration efforts to facilitate the use of expanded access programs. *J Clinical Oncology*, 33, 3979–3980.

¹⁰⁴ Food and Drug Administration, HHS (2009).

- Kolata, G. (1989). F.D.A. Approves the use of an experimental drug for AIDS patients' eye infections. *The New York Times*. Retrieved from <http://www.nytimes.com/1989/03/03/us/fda-approves-the-use-of-an-experimental-drug-for-aids-patients-eye-infections.html>.
- Mackey, T. K., & Schoenfeld, V. J. (2016). Going "social" to access experimental and potentially life-saving treatment: an assessment of the policy and online patient advocacy environment for expanded access. *BMC Medicine*, 14(1), 1.
- McDiarmid, J. (2014). Cobourg patient drew the 'short straw' in cancer drug trial. Retrieved from https://www.thestar.com/news/gta/2014/02/07/cobourg_woman_34_faces_death_from_melanoma_without_access_to_trial_drug.html.
- Mutual Pharmaceutical v. Bartlett, 133 S.Ct. 2466 (2013).
- Nichols E; Institute of Medicine (US) Roundtable for the Development of Drugs and Vaccines Against AIDS. Expanding Access to Investigational Therapies for HIV Infection and AIDS: March 12–13, 1990 Conference Summary. Washington (DC): National Academies Press (US); 1991. 1, Historical Perspective. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK234129/>.
- Ochs, Ashley. (2009). Study in Futility: Abigail Alliance for Better Access to Developmental Drugs Will Not Expand Access to Experimental Drugs for the Terminally Ill, A. *Seton Hall Law Review*, 39, 559.
- Okie, S. (2006). Access before approval—a right to take experimental drugs? *New England Journal of Medicine*, 355(5), 437–440.
- Proposed new drug, antibiotic and biologic drug product regulations, *Federal Register* 1983; 48:26729
- Pub. L. No. 114-255, 130 Stat. 1033 (2016).
- Qiu, X., Wong, G., Audet, J., Bello, A., Fernando, L., Alimonti, J. B., et al. (2014). Reversion of advanced Ebola virus disease in nonhuman primates with ZMapp. *Nature*, 514, 47–53. doi:10.1038/nature13777.
- Raus, K. (2016). An analysis of common ethical justifications for compassionate use programs for experimental drugs. *BMC Medical Ethics*, 17, 60. doi:10.1186/s12910-016-0145-x.
- Rid, A., & Emanuel, E. J. (2014). Ethical considerations of experimental interventions in the Ebola outbreak. *The Lancet*, 384(9957), 1896–1899. doi:10.1016/s0140-6736(14)61315-5.
- S.2912 Trickett Wendler Right to Try Act 2016, <https://www.congress.gov/bill/114th-congress/senate-bill/2912>. Sen. Johnson's prior attempt to move this legislation last year was blocked by then-Senate Minority Leader Harry Reid of Nevada.
- Sanghavi, D. M. (2013). The Pills of Last Resort: How Dying Patients Get Access to Experimental Drugs. *The New York Times*. Retrieved from <http://www.nytimes.com/2013/11/03/magazine/how-dying-patients-get-access-to-experimental-drugs.html?page-wanted=all&r=0>.
- Shire Policies: no access. (2016). *Shire Policies: Expanded access*. N.p., n.d. Web. 13 June 2016.
- Tenth Amendment Center. (2013). Right to Try. Retrieved from <http://tracking.tenthamendmentcenter.com/issues/right-to-try/>.
- United States v. Rutherford, 442 U.S. 544, 551-555 (1979)
- U.S. Department Health and Human Services. (2013). Guidance for Industry: Expanded Access to Investigation Drugs for Treatment Use – Qs & As 1.
- US Food and Drug Administration. (2013). IND Activity Reports. Expanded Access INDs and Protocols. <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/INDActivityReports/ucm373560.htm>.
- Walker, M. J., Rogers, W. A., & Entwistle, V. (2014). Ethical justifications for access to unapproved medical interventions: An argument for (limited) patient obligations. *The American Journal of Bioethics*, 14(11), 3–15.
- Young, F. E., Norris, J. A., Levitt, J. A., & Nightingale, S. L. (1988). The FDA's new procedures for the use of investigational drugs in treatment. *JAMA*, 259(15), 2267–2270. doi:10.1001/jama.1988.03720150043034.
- Zettler, P. J., & Greely, H. T. (2014). The strange allure of state "Right-to-Try" laws. *JAMA Internal Medicine*, 174(12), 1885–1886.