

Expanded Access — A Regulatory Balancing Act For Drug Cos.

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Consider this scenario. A patient (let's call him "X") suffers from a rare disease and is very sick. He has exhausted available therapies and his health is failing. A manufacturer is developing a therapy to treat Patient X's disease, but he does not qualify for the clinical trial and cannot wait for the drug's approval, which could be years away. Patient X is well educated and connected in the rare disease community. He has heard there may be a way to access this experimental therapy directly from the manufacturer — through the U.S. Food and Drug Administration's expanded access program (also known as compassionate use) with his physician's consent and assistance.

Should Patient X get the drug? What about other patients waiting for treatment who may not know about expanded access? What about patients who are enrolled in the clinical trial, but assigned to the placebo arm and therefore not benefiting from treatment? Can Patient X afford to pay for the drug? What about patients who can't afford to pay? What if Patient X's experience with the still experimental drug is negative and jeopardizes the clinical trial, preventing other patients from receiving the drug?

Manufacturers are increasingly facing these and other difficult questions as expanded access requests become more commonplace. The D.C. Circuit in *Abigail Alliance v. von Eschenbach*, 495 F.3d 695 (D.C. Cir. 2007) held that a terminally ill patient has no fundamental right to access post-Phase I investigational drugs. These requests are hard to dismiss and manufacturers face tough choices when deciding who, if anyone, should be granted expanded access to experimental therapies. They often must balance the needs of one patient with a heartbreaking story with the needs of a broader patient population eagerly awaiting an approved therapy. While FDA regulation and oversight provide some guidance to companies, many of the toughest questions are left for manufacturers to resolve on their own as they assess how to grant patients access to an experimental drug in a safe, fair and ethical manner outside the context of a clinical trial.

FDA Guidance

While the ultimate decision whether to provide an experimental drug rests with the manufacturer, any request for expanded access must first be submitted to and approved by the FDA.



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The regulatory pathway for expanded access is articulated in 21 C.F.R. § 312.300 — 21 C.F.R. § 312.320. The FDA's approval criteria is provided in § 312.305 and includes: (1) the patient has a serious or immediately life-threatening disease or condition and there is no satisfactory alternative; (2) the benefits of treatment exceed the risks and are not unreasonable; and (3) providing the investigational drug will not interfere or compromise the clinical trials to support marketing approval. Submissions to the FDA may be made through an existing investigational new drug (IND) application (often when requested by the drug manufacturer) or a new IND (often when requested by the treating physician who then acts as the sponsor).

The FDA divides expanded access into three categories: single patient use (which includes an emergency use protocol), intermediate-size patient populations and widespread use. We focus here on the single patient use and do not address the intermediate-size or widespread use processes. The FDA reports that of the single patient use expanded access requests it receives, it authorizes over 99 percent of them.

On June 2, 2016, the FDA's guidance on expanded access was bolstered by the publication of three new guidance documents, finalized after two years of circulation in draft form. The FDA has streamlined the application process for individual access requests and issued two Q&A guides: one clarifying some of the subtleties of the expanded access process and the other about charging for investigational drugs under an IND, including in expanded access situations.

Manufacturers' Risks and Challenges

Clinical Trial Enrollment

Expanded access requests raise a host of ethical, operational, business and logistical challenges for any drug manufacturer and particularly for smaller companies specializing in treatments for rare diseases. For example, rare disease companies may see a disproportionate number of requests for expanded access to drug, due to the lack of other available treatment options coupled with the severity of the disease involved. Additionally, the small patient populations associated with rare diseases pose particular challenges to evaluating expanded access requests as manufacturers in the space may already be hard pressed to find patients to enroll in their trials. Concerns that a patient with a rare disease may find it beneficial to bypass a trial to avoid the risk of receiving placebo and instead seek guaranteed treatment via expanded access are real. For a manufacturer already anxious to enroll a trial among a small patient population, expanded access could jeopardize its ability to fill the trial's necessary arms.

A manufacturer must also ensure that drug production is sufficient to cover expanded access requests in addition to the necessary doses for trial participants. Allocating expanded access drug to a patient who experiences a positive outcome could prompt a "run on the market" from other affected patients interested in obtaining promising treatment.

Impact of Adverse Events

A fear among drug manufacturers seeking marketing approval from the FDA is the effect of adverse events experienced by expanded access treatment. In cases of individual expanded access use, § 312.310(c)(2) requires the sponsor to provide the FDA with a summary of the expanded access use, including adverse events. The FDA notes that adverse event information under the expanded access program has been used only in a small number of cases to assess the safety of a drug.

However, the FDA reviewers consider the context of this adverse event data (e.g., outside the clinical

trial protocol and in patients with very serious or immediately life-threatening diseases). The FDA also has noted that expanded access INDs and protocols are unlikely to provide efficacy information useful to the FDA when considering the effectiveness of a drug. This may provide some level of comfort to companies concerned about the risk to ultimate FDA approval for their product, but the FDA has not yet gone so far as to say it will not consider the information as part of the approval process.

Potential PR Firestorms

The plea from the mother of a sick child on social media, urging a drug manufacturer to provide a drug, can quickly go viral. Such was the case when 7-year-old Josh Hardy's mother took to Facebook with the #SaveJosh campaign to persuade the drug maker Chimerix to provide its experimental antiviral drug brincidofovir (CMX001). The drug, then in Phase III trials for which Josh did not qualify, previously had been provided to a number of individuals via expanded access use.

However, the 50-person company with no marketed products had ceased the program, unable to juggle individual requests for expanded access with its increasingly expensive and time-consuming clinical trials. After death threats to CEO Kenneth Moch, intense public pressure and negative publicity, the company provided Josh with the drug and Moch resigned. This case highlights the juxtaposition between a personal quest to save the life of a child and the company's quandary, articulated by Moch as, "it's not just about Josh, it's about many Joshes."

Investor Claims

A manufacturer must also consider whether shareholder claims could result if an expanded access use negatively impacts the company, such as if clinical programs are delayed or terminated based on adverse events. Patient outcomes via expanded access use pose a risk of shareholder litigation if not reported carefully. In *Glaser v. Enzo Biochem Inc.*, 303 F. Supp. 2d 724 (E.D. Va. 2003), a shareholder suit was brought against company executives alleging that they made fraudulent statements that Phase II and Phase III would be fast-tracked based on the product's compassionate use experience. Although the court ultimately rejected this claim, the case identifies a risk that claims such as this may be alleged.

The U.S. Securities and Exchange Commission has also called attention to statements made by an executive about compassionate use. In *SEC v. Ferrone*, 2014 U.S. Dist. LEXIS 146359 (N.D. Ill. Oct. 10, 2014), the SEC claimed, and the court agreed, that an executive made false and misleading statements suggesting that FDA approval of the company's drug in a few cases of compassionate use indicated FDA approval to treat patients (he also failed to mention a clinical hold on the drug).

Industry Response: PhRMA and BIO Perspectives

Pharmaceutical Research and Manufacturers of America and the Biotechnology Innovation Organization have each published several statements discussing expanded access that track FDA regulations. They also raise additional equitable concerns. For instance, in a March 2014 statement on compassionate use, BIO cautions that emotionally charged and compelling individual patient cases may arise, but should be weighed against the obligations to large numbers of patients waiting for an approved drug.

State Right-to-Try Laws

Since 2014, 28 state legislatures have passed what are commonly referred to as "right to try" laws; 14

more considered similar legislation. These laws allow terminally ill patients, through their physicians, to request investigational drugs having successfully completed Phase I. Supporters argue that the FDA's expanded access program is burdensome and disproportionately favors industry interests over the rights of individuals to make personal medical decisions. Critics of right-to-try laws claim the laws offer false hope by suggesting that patients will receive miracle drugs. In reality, the laws do not require manufacturers to provide the drugs — they simply offer a right to ask, which is available through the FDA. Furthermore, the state laws are likely preempted by federal regulation.

This state activity has now led to federal legislative action. In May 2016, Sen. Ron Johnson, R-Wis., introduced S. 2912, a companion bill to the July 2015 House Bill H.R. 3012. Both bills would prohibit the federal government from taking action restricting access to investigational drugs otherwise accessible under state laws. The bills also address industry's concern that the FDA will unfairly consider adverse events in the drug's review and approval process. Introduced in May 2015, H. R. 6: The 21st Century Cures Act also addresses expanded access. H.R. 6 would require manufacturers to make their expanded access policies publicly accessible. H.R. 6 passed the House on July 10, 2015, but has yet to be taken up by the Senate.

Practical Tips

Companies who provide expanded access drugs, or contemplate doing so, should consider the following:

- Evaluate the manufacturer's capacity to provide expanded access drugs. This is especially important for small manufacturers. Before launching an expanded access program, consider if sufficient quantities of the drug can be produced without jeopardizing clinical trials. Consider if there is adequate staffing to evaluate and process requests. Determine whether the manufacturer intends to charge for expanded access drug and if so, if it is prepared to submit information required by the FDA for approval to charge.
- Create and publish a policy. A thoughtful policy articulating the criteria for assessing expanded access requests and providing product is an essential part of any expanded access program. Such a policy should be publicly available, reflect FDA expanded access regulations, and may include factors the company weighs in assessing requests, as well as the company's approach to charging for expanded access product.
- Internal review. A manufacturer should consider who is responsible for the review, approval and processing of expanded access requests. Legal, medical, regulatory and clinical representatives may lend helpful perspectives to decision-making. An individual or team with strong operational expertise might be tasked with specific responsibilities for fulfilling and documenting requests.

Expanded access plays a valuable role in the treatment of patients, but it is not without risks. Expanded access implicates significant ethical, business and legal considerations, which should be carefully and thoroughly vetted by all involved.

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