



Early Access Programs: Points to Consider¹

**BIO Board Standing Committee on Bioethics
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Patient requests for access to drugs and biologics prior to their approval has long created a dilemma for biotechnology companies. Typically, these requests come from seriously ill patients or their families who believe an experimental product could save or prolong their lives. However, biotech companies must balance those interests with their responsibility to move products through the regulatory process to receive marketing approval; a process that could be delayed or put at risk by providing access to the product outside of a clinical trial.

This issue's salience has grown over the past few years as patients and their advocates have increasingly argued that they have a "right" to unapproved products under certain conditions. This view has been promoted in recent litigation as well as legislation pending in Congress. FDA has issued new regulations in an attempt to mitigate this conflict.

The BIO Bioethics Committee has spent the past several months exploring the issues surrounding early access to biotech products. This document represents the Committee's deliberations and provides "Points to Consider" for biotechnology companies confronting these issues. It is the Committee's hope that these Points will help companies analyze the many ethical challenges raised by early access programs.

Background/FDA Rules on Expanded Access

FDA has a long history of permitting access to investigational drugs to treat patients with serious or immediately life-threatening diseases without adequate available therapy under special types of investigational new drug applications (INDs). The actions taken under these INDs were different from the studies covered under a "typical" IND because the treatment uses are not designed primarily to answer safety or effectiveness questions about the drug, but rather are intended to treat the patient.

¹ These Points to Consider were developed by the Biotechnology Industry Organization's (BIO's) Board Standing Committee on Bioethics [and approved on April 16, 2010]. This document does not represent BIO policy. It is intended for informational purposes and to further the debate on Early Access Programs.

On August 12, 2009 the FDA published two rules to clarify the methods available to seriously ill patients interested in gaining access to investigational drugs and biologics when such patients are not eligible to participate in a clinical trial and don't have other satisfactory treatment options.

The rule on "Expanded Access to Investigational Drugs for Treatment Use" aims to make investigational drugs more widely available to patients by clarifying procedures and standards. Under a rule promulgated in 1987, FDA stated that access to investigational drugs for a broad population could be authorized under a treatment protocol or treatment investigational new drug application (IND) when certain criteria were met. The 1987 rule implicitly acknowledged the existence of other kinds of treatment use, e.g. in individual patients, by adding a provision for obtaining an investigational drug for treatment use in an emergency situation.

The new rule provides more information about how experimental drugs can be made available to individual patients and intermediate-size patient populations. It also describes the criteria that must be met to authorize the expanded access use, for example:

- 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;
- 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
- 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.

The rule is available at <http://edocket.access.gpo.gov/2009/pdf/E9-19005.pdf>.

The other rule, "Charging for Investigational Drugs Under an Investigational New Drug Application", clarifies the specific circumstances and the types of costs for which a manufacturer can charge patients for an investigational drug when used as part of a clinical trial or when used outside the scope of a clinical trial. It is available at <http://edocket.access.gpo.gov/2009/pdf/E9-19004.pdf>.

Ethical Points to Consider

1. A patient's right to treatment based on his or her autonomous decision-making ability does not supersede a company's ethical responsibility to develop and market safe and effective products as fast as possible.

Patient autonomy

Many people argue that terminally ill patients have the right to an unapproved product outside the context of a clinical trial if they believe (and their physicians believe) it will treat their condition and if they understand the potential risks of taking the product. This perspective is

based on the principle that patients have the right of autonomy regarding their treatment. According to this view, as long as the patient understands the risks associated with that product – and the product has already demonstrated some evidence of safety – he or she should be allowed access.

This concept was most notably espoused by the petitioners in the case *Abigail Alliance v. von Eschenbach*. In that case, the Washington Legal Foundation on behalf of itself and the Abigail Alliance (the Alliance) sued to enjoin the FDA from barring the sale of post-Phase I drugs to terminally ill patients not in clinical trials. The Alliance claimed that the FDA's prohibition on the sale of post-Phase I drugs violated terminally ill patients' privacy and liberty rights. According to WLF, the FDA policy prohibited "mentally competent patients with no other treatment options from purchasing investigational drugs -- medicines showing initial evidence of safety and efficacy in clinical trials, but not yet approved -- even though their physicians recommend these drugs as their best hope of surviving or of prolonging their lives."

In granting the FDA's motion to dismiss, the district court held that the Alliance had failed to state a valid fundamental right to access. The court further reasoned that the FDA's policy bore a rational relationship to the legitimate state interest of public health. On appeal, a three-judge panel of the D.C. Circuit overruled the district court. It restricted its holding to terminally ill mentally competent adult patients for whom existing government-approved treatments were ineffective, but said that these patients had the fundamental right to access post-Phase I investigational new drugs determined to be sufficiently safe for expanded human testing.

Subsequently, in August 2007, the D.C. Circuit reversed that decision in an *en banc* opinion. The *en banc* court held that there was no fundamental right for terminally ill patients to access post-Phase I investigational new drugs. In so holding, the court noted that the democratic process rather than the courts should decide the broader issue of access to experimental drugs. The court said the FDA has statutory authority to regulate the right of individuals to access drugs, and that the FDA's approval process reflects definitions of safety and efficacy accepted by the scientific community. The Supreme Court declined to hear the case.

The Alliance and its supporters have subsequently taken this argument to Congress. The Compassionate Access Act of 2010, HR 4732, was introduced in March. The bill explicitly states that seriously ill patients have "a right to take actions to preserve their life by accessing available investigational drugs and biological products". The bill creates a new "Compassionate Access Investigational Approval" program by permitting the FDA to make products available under a treatment IND once the sponsor submits an application intended to provide "widespread access to an investigational drug, biological product, or device." FDA must make a rapid approval decision under this program and must use a standard based on whether "the totality of information available regarding safety or efficacy as compared to the risk of morbidity or death from a disease indicates a patient may obtain more benefit than risk if treated." If the potential risk to a patient of the disease outweighs the potential risk of the product and the product may possibly provide benefit to the patient, the FDA must approve the product.

The patient must provide written informed consent to receive the product. The manufacturer, distributor, sponsor and treating physician are immune from liability.

Companies have an ethical obligation to develop drugs and biologics for patient populations and bring them to market as fast as possible.

Autonomy in health care decisions is an important bioethics principle that has long been part of American law. It is manifested in the principle of – and legal requirement for – voluntary informed consent prior to health care treatment and participation in clinical trials.

However, this principle has been applied to ensure that patients cannot be forced to participate in experiments or to receive treatments against their will; not to assert that they have an affirmative right to an experimental treatment.

Moreover, there are competing and equally compelling ethical considerations involved in early access situations. For example, balanced against an individual's right to decisional autonomy is the company's ethical obligation to develop drugs for larger patient populations and to ensure these products meet regulatory approval as quickly as possible. Early access programs could create a conflict between these two principles since the company will be providing an unapproved product to a patient outside the scope of a clinical trial. Should an adverse event occur with a patient in the early access program, the company puts its broader clinical testing program at risk since the FDA may require the company to initiate new clinical trials or expand existing trials as part of its investigation of the event. This could delay or even prevent the approval of the product. Consequently, a larger patient population may be denied a potentially beneficial product.

In some circumstances, therefore, by allowing early access, the company risks market approval of the product. Thus, the question often confronting companies is whether to put an entire project at risk – and therefore jeopardize availability of a drug for a larger patient population – in order to provide early access to a product for an individual or small group of patients. The risk is compounded because it is uncertain whether the experimental product will be safe and effective for that patient.

The Committee is aware these situations are fact-specific and that the risks vary with each investigational product. Companies must balance these risks when developing an early access program.

2. Early access programs could hurt the integrity of the clinical trial process.

It has long been accepted that the clinical trial process is the best way to establish the safety and efficacy of drugs and biologics. The regulatory process contains numerous protections for research participants as well as strict safety and efficacy standards that must be met prior to marketing a product. These rules provide confidence to the public that research participants will not be forced to undergo unnecessary risk and that marketed products are safe and effective. The system relies on patient volunteers who, at least in part, are doing so to contribute to scientific knowledge that could benefit larger populations.

Early access programs could diminish the integrity of this system. If patients knew they could access products prior to approval outside the clinical trial process, it reduces their incentive to enroll in a trial especially since they may receive a placebo and therefore not be treated for their illness. Therefore, if early access programs become extremely common, the clinical trials system could break down, delaying or ending some product development programs.

3. A patient suffering from a life-threatening illness may not be able to provide consent that is truly informed when receiving a product under an early access program.

Early access programs such as those created in pending federal legislation rely on patients providing informed consent about the potential risks and benefits of an investigational product. This inherently implies that there is sufficient safety data available about a product to make an informed choice even though the product is still in development. Companies developing an early access program for a product must be confident that such data exists. They must also be careful that patients not get "false hope" from early product data.

4. If a company makes unapproved products available outside of a clinical trial, it must ensure equity in distribution.

If a company decides to make an unapproved product available, it must consider the process for determining which patients should have access to it. For example, certain patients may have an advantage over others because they know about early access programs, have hired outside counsel, or are particularly knowledgeable about research activities for a particular disease. None of these establish that patient as "more deserving" of early access to a product than others.

Therefore, a company needs to create appropriate inclusion/exclusion criteria for its early access program. These criteria should, to the greatest extent possible, ensure equity in availability and distribution of the product available under the early access program. If no such criteria can be developed, the company should re-consider whether to establish the program.