Background on Expanded Access to Investigational Pharmaceuticals

NORD’s Position: Time for Open-Minded Discussion of Expanded Access

NORD recognizes the complexity of the expanded access issue, and understands and has sympathy for the willingness of some terminally-ill patients to take risks in using experimental treatments that are not yet completely tested. At the same time, it recognizes the legitimate interests of the government in seeking to systematically oversee the drug development and approval process. NORD also recognizes that other parties, such as the drug companies, must navigate requests for expanded access carefully. Finally, NORD understands that other entities also play a role, such as the IRBs, which are charged with protecting patients, and insurers who are responsible for reimbursing the legitimate medical expenses of their policy-holders.

NORD’s interest is in evaluating proposals to see how they would affect the rare disease patient population. The patient’s interests and well-being is always at the center of NORD advocacy. If specific changes—administrative or legislative—in the expanded access process might be beneficial to patients without exposing them to unreasonable risks or dismantling the system that is in place to accelerate the discovery, approval and delivery of safe and effective drugs for millions of Americans, then NORD will give serious consideration to supporting such proposals.

Meantime, NORD encourages public discussion, debate, and proposals for constructive improvements to the expanded access system.

Defining the Issues: Complex Interactions/Competing Public Goals

There are a number of instances where patients have come forward requesting a company to provide expanded access to an unproven drug. How should a company respond when a patient wants to try a drug that is not yet proven safe or effective? Sometimes companies have been able to accommodate the patient, in coordination with their physician and the FDA. Other times, the company did not have sufficient stock of the drug, could not afford to provide access, felt the data was too incomplete for use outside a trial or was concerned that use outside the trial might threaten the viability of ongoing and planned clinical trials of the drug.

Of even greater complexity: what position should the FDA take, given one of its fundamental roles is to assure that medicines are proven safe and effective before they are used outside of an authorized clinical trial? Currently, FDA runs a limited, carefully
controlled expanded access program that meets some of the demand, but clearly not all of it. On its own initiative or in response to Congress, should FDA alter its policies to provide a broader array of acceptable situations? There are a number of ways that this might be done—but much of the discussion focuses on altering the risk-benefit standard applied to expanded access requests and/or finding ways to make the existing program more efficient and less-time consuming.

Examining these questions requires an understanding of how the current system operates. All new drugs go through three phases of testing. Once the testing is done and the data are collected, the FDA must decide whether the drug is safe and effective, and whether the benefits to patients outweigh the risks. Since every drug has some risk, this is always a challenging decision.

The term “expanded access” is used to describe the process by which an investigational drug can become available to a patient while the drug is still being studied and before the approval process is complete.

Patients wishing to obtain a drug through the expanded access system must go through a well-defined process. First, a physician must prescribe the investigational therapy, and in doing so, must believe the benefits of taking the experimental therapy outweigh the potential risks. The physician must believe that all other treatment options are not viable for this patient. Finally, the physician must also recommend a treatment regimen that the physician will oversee.

Once the physician requests access to the experimental therapy for his or her patient, the pharmaceutical company must assess the physician’s risk-benefit analysis, alternative therapy analysis, and treatment plan. If the company agrees with the physician’s assessment, and is willing to provide the treatment to the patient, the physician and company will file an IND form with the FDA to allow the investigational product to be used by the patient.

The FDA must then also confirm that the benefit of taking the investigational therapy outweighs the potential risks for that patient, that other treatment options are not comparable or satisfactory, and that the patient has a serious or life-threatening illness.

The FDA is often criticized for not approving expanded access requests, but in fact the FDA says it has approved almost every request, denying only a handful of the approximately one thousand requests submitted each year. The FDA must deny access to an unproven drug if there is a possibility the drug may cause more harm than good for the patient.

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1 U.S. Food and Drug Administration. (2013). Guidance for Industry: Expanded Access to Investigational Drugs for Treatment Use – Qs & As. Silver Spring, MD
2 Ibid.
Another player in the expanded access process is an Institutional Review Board (IRB). This is a diverse group of medical and scientific professionals and trained volunteers charged with assuring that only ethical research is conducted and that researchers fully comply with informed consent. Even if the FDA and the sponsor agree that expanded access is appropriate for a patient, it may take several months for an IRB to review the proposal, as the FDA requires the approval of a convened IRB in which the majority of IRB members are present. Many full IRBs take months to deliver a decision. Access to IRBs is limited in many rural and underserved areas.

In sum, for an expanded access request to be granted:

- a patient and physician must determine that a particular experimental therapy meets a patient's dire (terminally ill) needs;
- the manufacturer must agree to provide the product;
- the FDA must concur; and
- an IRB must approve.

Companies often agree to legitimate requests, but they also have a number of concerns about participating. For example, companies may be concerned that an adverse event in a patient using the drug as part of an expanded access program may derail the entire drug approval process because the FDA retains the right to use data from expanded access cases when reviewing a drug.

There are also various liability issues for a drug company when providing a drug in an expanded access program. And sometimes sponsors may simply not have enough of the investigational drug to give to patients outside of the clinical trials. In addition, increased use of investigational drugs outside of the clinical trial setting makes it more difficult to find patients for the clinical trial, as many do not want to risk receiving the placebo therapy. This is especially challenging for a drug intended to treat a rare disease, where the number of patients eligible for a study is small. Finally, companies are only allowed to be reimbursed for distributing the drug under an expanded access program in very limited and specific cases.

**Avenues for Consideration:**

Traditionally, the debate over access to experimental therapies has focused on three issues:

- Should FDA grant more or less access based on changes that might be made in the risk-benefit standard it applies?

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6 21 CFR 312, Subpart I
• Is there a constitutional “right” to access to experimental drugs?
• Can the process be made more efficient without compromising any safeguards?

While a “constitutional right” to a therapy has largely been resolved by the courts, and the FDA’s Risk-Benefit formula should always be examined for opportunities for improvement, NORD believes that our best opportunity to improve the expanded access system lies elsewhere. For example, additional ways might be explored to see whether and how FDA can expedite its process for reviewing applications for expanded access. Educational programs for physicians and IRBs could be undertaken so that they can engage in the process more efficiently. A central navigator service for patients looking to utilize expanded access programs could be explored. Finally, incentives could be created to reward companies who agree to provide investigational drugs. These are the types of ideas that merit further discussion.

One proposal put forth that claims to solve this problem is the “Right-to-Try” legislation introduced in several state legislatures. These have been recently enacted in Colorado, Louisiana, and Missouri. These laws, a model of which was drafted by the Goldwater Institute, would allow companies to distribute a product to patients once FDA-approved phase 1 drug trials have been completed and the product is officially in an FDA-approved clinical trial.

Proponents of the law claim that “Right-to-Try” will allow companies to provide their experimental products to terminally ill patients without concern of punitive FDA actions. However, opponents of the initiative point out that the “Right-to-Try” laws do not remove the barriers cited by the pharmaceutical companies in rejecting expanded access requests, including a limited supply of the drug, the cost of manufacturing extra product outside of the clinical trial, disincentives for enrolling in the clinical trial, and possible adverse events that may compromise the trial. Finally, the “Right-to-Try” laws do not force companies to provide their product to patients, thus allowing companies to use the same rationales already used to decline an expanded access request.

The “Right-to-Try” laws do provide a carefully-defined “safe harbor” within states for terminally ill patients, physicians, and drug companies to agree upon access without fear of state laws being enforced against them (e.g. state medical practice and liability laws).

On the issue of expanded access, there are no easy answers. NORD encourages public discussion, debate, and proposals for constructive improvements to the expanded access system.

For questions regarding NORD or its work on expanded access issues, please contact Diane Dorman, Vice President of Public Policy, at ddorman@rarediseases.org or (202) 588-5700 ext. 102.