

Principles for Access to Unapproved Therapies

As policy makers debate potential changes to the way in which unapproved therapies are accessed, the undersigned organizations believe that changes should adhere to the principles outlined below.

Alliance for Aging Research
American Cancer Society Cancer Action Network
American Society of Clinical Oncology
American Society of Pediatric Hematology/Oncology
Association of Pediatric Hematology/Oncology Nurses
Cancer Support Community
Children's Cause for Cancer Advocacy
Friends of Cancer Research
Leukemia & Lymphoma Society

Metastatic Breast Cancer Network
National Coalition for Cancer Research (NCCR)
National Comprehensive Cancer Network
National Organization for Rare Disorders
National Patient Advocate Foundation
Parent Project Muscular Dystrophy
Prostate Cancer Foundation
St. Baldrick's Foundation
Susan G. Komen

Role of research and therapy development

- The goal of therapy development is broad patient access to safe and effective treatments.
- High-quality basic and translational research will lead to improved treatments for disease.
- Clinical research involves the systematic collection of outcomes data from experimental treatments.
- FDA approval is the only way to provide public access to therapies proven to be safe and effective.
- Patients should have access to clinical trials for their disease.
- Sponsors should do everything they can to structure the exclusion/inclusion criteria of clinical trials to accurately represent the population most likely to benefit from the therapy with considerations for different characteristics that may include age, ethnicity, and sex. In addition, the FDA should facilitate and encourage sponsors to structure their trials in this manner.
- The conduct of research should follow established ethical guidelines.

Role of expanded access to unapproved therapies

- Individuals unable to participate in a clinical trial and who have exhausted other viable options should be able to access unapproved therapies following the same established ethical guidelines as required within a clinical trial, which include:
 - Independent evaluation of the ethics and conduct of the expanded access by a competent authority familiar with the natural history of the condition,
 - Informed consent of the person taking the experimental treatment,
 - Medical equipoise with ethical consideration for the existing treatment options,
 - Absence of coercion,
 - Prospect of benefit for patients and society.

- Institutional Review Boards (IRBs) should review both emergency and non-emergency access requests for unapproved therapies in a timely manner, and should be accessible to all patients and physicians wishing to pursue access to such therapies.
- Access to unapproved therapies through means other than clinical trials should be the exception rather than the rule.
- Access to unapproved therapies outside of a clinical trial should not hamper the conduct of clinical trials.
- The FDA plays a critical role in assessing the risk/benefit ratio of an unapproved therapy, determining whether clinical trials will not be harmed by access to unapproved therapies, and reviewing data that is collected from the use of the therapy, and must be included in these deliberations.
- Expanded access policies should not allow sponsors, individual doctors, or institutions to exploit patients seeking access to unapproved therapies
- Sponsors should respond to requests for unapproved therapies in a timely manner considering the severity of the disease and in an equitable way that does not favor certain groups or individuals based on non-medical information. Selection criteria should be rational and be applied uniformly.
- Sponsors should have clear expanded access policies and make these public (for example on a company's website) along with appropriate contact information.
- Sponsors, as the party with the most information on the safety, efficacy, and availability of their products, must always be included in the deliberations and decisions regarding access to their unapproved product outside of a clinical trial.
- Sponsors should consider the potential for expanded access demand when considering the production needs for the experimental therapy as part of a clinical trial.

Background on expanded access to experimental drugs

As policymakers consider changes to the current process, it is important to understand the history of the current protections in place to protect patients. The current landscape of access to experimental drugs is the result of actions taken over the years to address issues of safety, ethics and access.

History of regulation

In the U.S., drugs intended to treat diseases must be tested in controlled settings and proven safe and efficacious before they are allowed to be sold and prescribed to the public. This was not always the case. Over a century ago, many drugs were manufactured and marketed to treat diseases with insufficient, or in some cases, no evidence that they were effective in treating the diseases that they claimed to treat, and also without proof that the drugs did not actually cause more harm to the person taking them than by not taking them. In fact, some early “drugs” contained opium, heroin, mercury, and other compounds now known to be dangerous or toxic.

Responding to a series of incidents that caused public outrage, several laws were enacted in the 20th Century, resulting in the modern FDA oversight paradigm for drugs. Drug safety requirements were enacted in 1938 after 107 deaths, including 30 children, were caused when an antibiotic was reformulated from a pill to a liquid using the poisonous diethylene glycol to dissolve the drug. It wasn't until 1962, when thalidomide was found to have caused birth defects in Europe, that a law was passed to not only require drugs to be safe, but also to require for the first time, proof of efficacy before a drug could be approved. Notably, thalidomide was not approved in the U.S. because a medical officer at FDA refused to approve the drug, a decision that at the time was criticized at the time as obstructionist.

With the current system in place, Americans have come to expect that approved prescription drugs are safe and effective for the diseases they claim to treat. The U.S. drug approval process is recognized as the gold standard worldwide for ensuring safety and efficacy.

Expanded access to unapproved drugs

Unapproved drugs are generally only available to individuals through participation in a clinical trial, where they are tested in a controlled setting to evaluate safety and efficacy. However, there is a process to allow the use of an experimental drug outside of a clinical trial in what is known as “compassionate use,” or “expanded access” for very sick patients with no other treatment options. The FDA expanded access program was created largely due to activism in the 1980s tied to the development of new therapies for HIV/AIDS patients and is a structured program.

Performance of existing FDA expanded access program

Evaluation of FDA's performance reviewing expanded access applications for the 10-year period from January 2004 to December 2015 show that nearly 11,000 individual expanded access applications were processed by FDA, of which 99.7 percent were approved. One oft-cited concern expressed about involving FDA in expanded access decisions is that they may hold patient deaths or adverse events against the experimental drug and halt clinical trials. During this 10-year period, two trials were temporarily halted due to patient deaths, but were eventually allowed to proceed. These two cases

represent a hold rate of 0.2% due to adverse events related to expanded access. By comparison, 7.9 percent of all open drug development programs have been subject to similar clinical holds for other reason that have nothing to do with expanded access.¹

Recent Developments

Notably, two recent policy changes have been made and it is still too early to assess the impact on requests. In 2016 FDA rolled out a simplified expanded access form that is estimated to only take 45 minutes to fill out. Previously the form was the same one used for a full clinical trial and was much more confusing and involved more effort. Secondly, a provision in the 21st Century Cures Act now requires drug sponsors to make their expanded access policies and contact information publicly available on their websites once a drug candidate is in a phase II or later trial.

Challenges

For expanded access to a drug to occur, numerous parties must agree to it, and each faces challenges. Those challenges are outlined below by stakeholder.

Drug sponsor

- **Appropriateness**—Not all patients requesting access to an experimental drug may match the intended use of an experimental drug.
- **Drug supply**—Experimental drugs are sometimes made in limited quantities solely for research needs, leaving insufficient quantities of the drug for compassionate use.
- **Ethics of selection**—If a sponsor offers drugs to individuals outside of a clinical trial, decisions should be based on sound criteria and applied equitably to all requestors in order to be ethical.
- **Role of adverse events**—Patients requesting expanded access are often very sick, any adverse events attributed to the investigational drug (e.g. stroke, heart attack, deaths) as part of expanded access could jeopardize the drug’s chances of full approval.

Patients

- **Cost issues**—Insurance companies typically exclude unapproved drugs from coverage, so treatment through compassionate use may result in patient out-of-pocket costs for both the drug, which manufacturers are allowed to charge for, and for associated physician services.

Doctors

- **Data on safety and efficacy**—More is known about an experimental drug the longer it is studied; however, not all clinical trial data are necessarily made publicly available early in a drug’s development, meaning that individual physicians may have limited data about a drug on which to base decisions about the clinical appropriateness and safety for compassionate use with their patients. Most phase I and II drugs ultimately do not receive FDA approval

Table 1: Drugs entering clinical phase of research that ultimately reach full FDA approval

Phase I	15%	Phase II	23%	Phase III	58%
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Source: Hay, M. Thomas, DW. Craighead, JL, et al., *Clinical development success rates for investigational drugs*, *Nature Biotechnology*, 32(1), Jan 2014.

¹ Jarow JP, Lemery S, et al., “Expanded Access of Investigational Drugs: The Experience of the Center of Drug Evaluation and Research Over a 10-Year Period,” *Therapeutic Innovation & Regulatory Science*, Vol. 50(6), 705-709, 2016.