HHS Public Access

Author manuscript

Ther Innov Regul Sci. Author manuscript; available in PMC 2017 May 24.

Published in final edited form as:

Ther Innov Regul Sci. 2017 March 1; 51(2): 177–179. doi:10.1177/2168479017694850.

Overview of FDA's Expanded Access Program for Investigational Drugs

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Abstract

Expanded access, also called "compassionate use," provides a pathway for patients to gain access to investigational drugs, biologics, and medical devices used to diagnose, monitor, or treat patients with serious diseases or conditions for which there are no comparable or satisfactory therapy options available outside of clinical trials. The US Food and Drug Administration (FDA) facilitates the expanded access process; however, access to investigational treatments requires not only FDA's review and authorization but also the active involvement and cooperation of other parties, including drug companies and health care providers, in order to be successful.

Keywords

expanded access; investigational new drug; single patient expanded access; investigational therapies

Introduction

Expanded access is the use of an investigational new drug outside of a clinical trial in patients for the diagnosis, monitoring, or treatment of a serious disease or condition. In contrast, participants in clinical trials/studies are considered human subjects, whether they are patients or healthy volunteers. The Food and Drug Administration's (FDA's) history of facilitating access to investigational therapies reaches back to the 1970s; however, regulations did not specifically describe a pathway for access to unapproved drugs until 1987.[1] FDA later published revised regulations in 2009, further clarifying the expanded access process.[2]

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The views expressed in this article are those of the authors and not necessarily those of the U.S. Food and Drug Administration.

Declaration of Conflicting Interests

No potential conflicts were declared.

There are certain requirements that apply to all three types of expanded access (individual patient (including emergency use), intermediate-size patient population, and expanded access for widespread treatment use) under a treatment Investigational New Drug (IND) application[3]: the patient must have a serious or immediately life-threatening disease or condition and have no comparable or satisfactory alternative therapy; the potential benefit must justify the potential risks of the treatment; and providing the drug must not interfere with or compromise the drug development program. The primary difference in the three types of access is the number of patients participating. A widespread treatment IND is typically used to provide access to a large population and is often used to bridge the gap between completion of clinical trials and marketing approval. An intermediate-size population IND has no fixed numerical requirement, but it is for more than one patient and is generally employed when the investigational drug is not actively being developed for marketing. Individual patient expanded access is employed for the medical management of a single patient and is the preferred mechanism for providing access in an emergency setting. It is this third form of expanded access that is the focus of much of the public debate and the remainder of this article.

Individual Patient Access to Investigational Drugs

In recent years, there has been an increased interest in expanded access from both the general public and lawmakers. Since 2009, social media have amplified campaigns and online petitions requesting that certain individuals get access to experimental medications under FDA's expanded access procedures. These campaigns often describe a family's tragic situation to pressure a drug company into providing an investigational treatment,[4] garnering sympathy for the families and placing pressure on both the drug company and FDA and highlighting the ethical challenges of expanded access.[5] In addition, state lawmakers continue to introduce and pass right-to-try laws that would allow companies to provide access to investigational drugs without FDA oversight.[6,7]

FDA fully supports patient access to investigational drugs for those most in need. Nevertheless, enrollment in clinical trials is the preferred option, whenever possible, for patients wishing to gain access to investigational drugs. Clinical trials ensure adequate patient protection and are the best mechanism to provide the evidence of safety and effectiveness required to determine whether the drug should be marketed. Diversion of eligible patients from actively enrolling in clinical trials could impede development and delay or prevent the public at large from having access to a potentially effective drug, particularly for rare diseases. Clinical trials are the basis for marketing authorization and are the most efficient means to make safe and effective treatments available to the largest number of patients.

Expanded access for individual patients depends on the cooperation and expertise of many. The physician (who applies on behalf of the patient), the drug company, the institutional review board (IRB), and the FDA all have important roles and must work together for the expanded access process to succeed. The patient's physician should first contact the drug company to ensure it is willing to provide the drug. Once the company has agreed, the physician must obtain IRB approval and apply to the FDA. For emergencies that require

treatment before a written request can be submitted, FDA may authorize the emergency use over the telephone or through other means of electronic communication. A written request must be submitted afterwards, but the physician must obtain informed consent from the patient prior to administering the investigational drug.

Expanded access can only occur if a drug company agrees to provide the investigational drug. FDA authorized 99% of single patient expanded access applications in FY2010–2015.[8] FDA cannot require a manufacturer to provide its drug,[9] and there are valid reasons why a manufacturer may not do so, such as an ongoing clinical trial the patient can join and limited drug supply. The fear that adverse events that occur during expanded access will lead to clinical holds and have an unfavorable impact upon the overall drug development program is a concern sometimes raised. A review of almost 11,000 expanded access requests over a 10-year period, however, demonstrated that only two drug development programs were placed on clinical hold due to adverse events observed in patients receiving expanded access, and even these were temporary.[10] Therefore, it is very rare for an adverse event occurring during expanded access to adversely affect drug development.

Recent Updates and FDA's Role

At FDA's Center for Drug Evaluation and Research (CDER) and its Center for Biologics Evaluation and Research combined, FDA receives over 1000 requests for all types of expanded access per year. For requests submitted to CDER's review divisions, the median time to proceed is 4 days for non-emergency expanded access requests and less than 1 day for emergency requests. FDA has recently streamlined the process that physicians use to request expanded access for individual patients so that it takes an estimated 45 minutes to complete the current FDA application form, Form FDA 3926.[11]

In addition, FDA recently published 3 final guidances on expanded access.[9,12,13] The first guidance describes Form FDA 3926 and the process for licensed physicians to request expanded access to an investigational new drug for individual patients outside of a clinical investigation. The second guidance clarifies the circumstances under which FDA authorizes charging for an investigational drug in both clinical trials and under expanded access for treatment use, and clarifies which costs can be recovered. The third guidance provides detailed information about implementation of FDA's regulations on expanded access to investigational drugs, including how expanded access is defined, when and how to request expanded access, and what information should be included in such requests. At the same time the guidances were published, FDA improved its website, adding information from its Center for Devices and Radiological Health, and produced information sheets for patients and physicians.[14–16]

FDA has dedicated staff in the Office of Health and Constituent Affairs and CDER's Office of Communications, Division of Drug Information, to assist physicians and patients who are navigating the expanded access system. They help direct interested parties to the sponsors of investigational drugs so that these sponsors can explain their expanded access policies. In addition, they can provide information on IRB resources for those that do not have access to

a local IRB. The staff is also able to assist in identifying actively enrolling clinical trials and facilitating requests with the appropriate review divisions within the Agency.

Although FDA approves the overwhelming majority of applications, it often requests modifications to the protocol to ensure patient safety. Internal FDA studies show that changes to the dose of the investigational drug, safety monitoring of the patient, and/or the contents of the informed consent form were required for 11% of applications before allowing the IND to proceed.[17] FDA review staff are uniquely positioned to conduct these reviews because our assessment of expanded access requests takes into account data and information that is often unavailable to others. FDA also provides a bulwark against exploitation of vulnerable patients and ensures that IRB review will be obtained.

Providing an investigational drug is not always in the best interest of the patient or the public health. These ethical and practical challenges require the continued resources, cooperation, and expertise of all involved. FDA's staff will continue their commitment to expedite access to investigational treatment, when appropriate, while ensuring that the patient is protected and that clinical development is not compromised.

Acknowledgments

Funding

No financial support of the research, authorship, and/or publication of this article was declared.

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