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TRANSLATIONAL TOOLBOX

Expanding Patient Access to Investigational Drugs

Single Patient Investigational New Drug and the "Right to Try"

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SUMMARY

With drug approval times taking an average of 8 years from entry into clinical trials to full U.S. Food and Drug Administration (FDA) approval, patients with life-threatening and severely debilitating disease and no reasonable therapeutic options are advocating for expanded access (EA) to investigational drugs prior to approval. Special investigational new drug (IND) application categories allow patients who meet specific criteria to receive treatment with non-approved drugs. The FDA approves over 99% of all single-patient INDs, providing emergency approval within hours, and non-emergency approval within an average of 4 days. "Right-to-try" laws passed in 38 states would allow patients to bypass FDA processes altogether, but contain controversial provisions that some claim risk more harm than benefit to desperate and vulnerable patients. This review focuses on FDA EA to non-approved drugs through a special category of IND—the single-patient IND—and "right-to-try" (R2T) access outside of the FDA. (J Am Coll Cardiol Basic Trans Science 2018;3:280–93)

Answering a call to curb interstate market for adulterated and/or mishandled food and pharmaceuticals, the Federal Food, Drug and Cosmetics Act of 1938 required safety approval of all drugs by the FDA prior to marketing (1). Later amendments to federal law required that a drug must be proven effective as well as safe before marketing in the United States (2). The FDA is now among the largest of consumer protection agencies in the world, balancing increasing pressure to expedite the development and release of new and effective therapies to patients, against a mission to simultaneously minimize harm. Meanwhile, drug innovation, at least for some classes of drugs such as cardiovascular therapies, is slowing (3), and the costs of drug development are skyrocketing. Public pressure to expedite the deployment of new medical therapeutics has led to numerous recent legislative interventions.

Once drugs have passed preclinical conceptualization, manufacture, in vitro testing and in vivo animal testing, they enter the phase of development that requires in-human demonstration of safety and efficacy for their intended purpose. In order to enter this critical and costly development stage, drugs must be filed with the FDA (the investigational new drug [IND] filing), so that the agency can monitor in-human testing via periodic reports, inspections and audits as the entity progresses through clinical trials before an application is submitted for FDA marketing approval and the drug becomes generally available to the public.

Recent federal legislation seeking to expedite drug deployment to patients may significantly affect how such therapeutics enter the FDA processes and how

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soon they reach the public. This article discusses the FDA process for individual patient access to non-approved drugs, and explores "right-to-try" (R2T) legislation that is intended to facilitate the entry of new therapeutics into clinical use prior to full FDA approval.

INVESTIGATIONAL NEW DRUG INDs

The basic IND filing is a request for FDA authorization A to administer a non-approved drug or biological product to humans so that evidence of efficacy and safety can be obtained for marketing approval. In addition, federal law requires that a drug be the subject of an approved marketing application before it can be transported or distributed across state lines. Long before FDA approval, the drug developer will usually want to ship the drug to clinical investigators in multiple states, and they must obtain an exemption from that law. The IND application provides the means by which a drug sponsor can acquire this exemption (4). Thirty days after the sponsor files an IND application, unless prevented by a directive from the FDA, they may begin the long process of clinical testing. The average time to complete all phases of clinical trials is approximately 8 years (1).

In many cases, drugs may be able to enter clinical use before achieving full FDA approval, through special expanded access (EA) IND filings. In addition, most states have now passed R2T legislation aimed at guaranteeing that certain patients can receive experimental therapies without going through the FDA, before full FDA approval has been granted.

INDs have 2 major classifications—research or commercial—depending upon the sponsor for the drug development and intended destination of the drug. The FDA defines an IND as commercial if the sponsor is a corporate entity or 1 of the institutes of the National Institutes of Health (NIH), or if it is clear that the drug may eventually become commercialized (5). The IND is called a research IND if the drug is sponsored by an individual. Within both the research and commercial INDs are IND subcategories. The "investigator IND" is the most common type of research or commercial IND, in which the investigator initiates and conducts studies and provides immediate supervision of the study drug. A more detailed review of the Investigator IND application process has been published previously (1).

FDA EXPANDED ACCESS INDs FOR NONAPPROVED DRUGS

The FDA began facilitating access to non-approved drugs in the 1970s, although it took until 1987 for a specific pathway for such access to be developed (6). Revised regulations regarding EA access to investigational drugs were published in 2009, with revised guidance for industry update as recently as October 2017 (7).

FDA EA falls into 3 categories: 1) individual access to INDs, including emergency use (EIND); 2) access for intermediate-size patient populations; and 3) widespread treatment use, or treatment investigational new drugs (TIND) (7,8). Certain requirements apply to all 3 categories: 1) the patient must have a serious or immediately life-threatening disease or condition, and have no comparable therapy or satisfactory alternative therapy; 2) the potential benefit must justify the potential risks of the treatment; and 3) providing the treatment must not interfere with or compromise the drug development program (e.g., by critically depleting a supply of a drug that is needed for conducting clinical studies) (9).

The "widespread" TIND is typically obtained to bridge the gap between completion of clinical trials and full FDA approval. Patients in phase 3 clinical trials who are benefitting from the new drug, for example, may be allowed to continue treatment after study completion while full approval is obtained (10). An intermediate-size treatment IND has no specific population size definition, but is used when more than 1 patient will be treated, or when the drug is not being actively developed for market. An intermediate-size early access IND might be created by consolidating multiple single-patient IND requests for the same drug. An individual, or single-patient IND allows treatment of a single patient with a non-approved drug. The EIND is a subcategory of the individual patient IND, for when a patient requires emergency treatment and cannot wait for the FDA 30-day review period. The evidentiary threshold to prove to the FDA's satisfaction that benefits outweigh the harms are higher as more patients are involved in the IND. Thus, a widespread or intermediate-size treatment IND may require significant clinical evidence in the form of studies, while for a single-patient IND the physician need only conclude that the drug does not pose greater risk than the disease itself (10).

THE SINGLE PATIENT IND

With rare exceptions, commercial sponsors do not apply for individual patient INDs, since it is rare for a commercial entity to directly oversee the treatment of an individual patient. Although the manufacturer will have an IND filing with the FDA to conduct

ABBREVIATIONS AND ACRONYMS

EAP = expanded access program

EIND = emergency investigational new drug

FDA = U.S. Food and Drug Administration

IND = investigational new drug (filing)

IRB = institutional review board

LOA = letter of authorization

R2T = right-to-try

TIND = treatment investigational new drug