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TRANSLATIONAL TOOLBOX

Expanding Patient Access to Investigational New Drugs

Overview of Intermediate and Widespread Treatment Investigational New Drugs, and Emergency Authorization in Public Health Emergencies

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SUMMARY

Individual patients with life-threatening or severely debilitating diseases can petition the U.S. Food and Drug Administration (FDA) through their physicians to have expanded access (EA) to drugs that are in clinical trials but have not reached full FDA approval (the "single-patient" investigational new drug [IND] application). Additionally, recent state and federal laws—so-called "right to try legislation"—allow patients to approach drug companies directly for access prior to FDA approval. While these pathways provide potential access for individual patients to investigational drugs, different EA pathways permit entire groups of certain patients to access investigational drugs prior to FDA approval. This review focuses on special categories of EA INDs intended for multiple patients—the intermediate-group IND and the widespread-treatment IND—as well as emergency authorization for use of investigational drugs and biological products (e.g., vaccines) in public health emergencies. (J Am Coll Cardiol Basic Trans Science 2018;3:403–14) © 2018 The Author. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

U.S. Food and Drug Administration (FDA) approval is required for interstate transport and marketing of drugs for human consumption in the United States (1,2). The FDA approval process begins when an investigational new drug (IND) is filed with the FDA. The IND filing provides the drug investigators with an exemption to the law prohibiting interstate transport of nonapproved drugs so that investigational substances can be distributed to researchers. It also launches FDA monitoring of in-human testing, through periodic reports, inspections, and audits throughout clinical trials to demonstrate efficacy and safety in humans. Drug testing can begin 30 days after an IND filing unless the FDA objects. Thereafter, the average time for completion of all clinical trials is about 8 years (1,3).

For patients with life-threatening or severely debilitating disease, the wait for approval is simply too long, and can both abolish hope for those who diseases will be quickly fatal, and lead to sustained or even permanent disability for those whose diseases linger but are without effective proven therapies. Spurred by patient advocacy during the early days of the acquired immunodeficiency syndrome (AIDS) epidemic in the late 1980s, and facilitated by subsequent legislative efforts over the next 20 years, regulatory initiatives permit the FDA to release drugs for use in individual patients through expanded access

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ABBREVIATIONS AND ACRONYMS

CMV = cytomegalovirus

EA = expanded access

EUA = emergency use authorization

FDA = U.S. Food and Drug Administration

IND = investigational new drug

REMS = risk evaluation and mitigation strategy

STEPS = System for Thalidomide Education and Prescribing Safety program

(EA) INDs (4,5), in many cases allowing emergency treatment with nonapproved drugs within hours of application, and nonemergency treatment within an average of 4 days (6). Further, most states have enacted so-called "right to try" legislation, permitting "compassionate use" of investigational drugs by individual patients through applications directly to the manufacturer (6). It should be noted that although the terms "compassionate use" or "preapproval access" are often used informally to refer to the use of an investigational drug to treat a patient outside of a clinical trial, these terms are not defined or described in FDA regulations, which simply refer to expanded access to investigational drugs.

The call for EA is not limited to individual patients. Advocacy organizations have pressed for groups of patients with rare and/or "orphan" diseases, for example, to be able to access promising new therapies prior to their approval. Indeed, social media is increasingly becoming a consumer/patient advocacy tool for implementing FDA regulatory changes and promoting access to investigational therapeutics (7). In addition, once a drug has completed phase 3 testing and is awaiting approval, patients who have benefited from in-trial treatments may want continued therapy, and such use requires some form of "bridging approval" from the FDA to allow potentially large groups of patients to continue treatment while final FDA approval is pending.

A previous review discussed individual patient emergency and nonemergency access to investigational drugs (6). This review will focus on FDA EA for intermediate-sized groups of patients (the "intermediate-sized IND") and EA for entire classes of patients (the "widespread treatment use" IND), as well as emergency release of investigational drugs and biologics for use in public health emergencies.

PITFALLS IN COMPASSIONATE USE

Releasing investigational new drugs to individual patients who are facing certain death or disability seems to be a relatively uncomplicated decision, but allowing EA to entire groups of patients for treatment with an investigational new drug presents more complex regulatory, logistical, and ethical challenges for scientists, commercial entities, and the FDA. The current regulatory process from IND filing to drug approval has evolved and includes not only the FDA's historical primary mission of ensuring patient safety, but also, since the latter half of the 20th century, the newer mission of ensuring that marketed drugs are actually efficacious for their advertised/approved use. EA for a single patient may not present much of a challenge to the assertion that a drug's benefits outweigh the risks, because as presumably the patient requesting compassionate use faces an otherwise dismal clinical future, taking even significant risks with a new drug still presents potential benefits to a patient without other options. Early in a drug's regulatory pathway, however, it is not usually possible to ensure that a drug has a reasonable risk/benefit ratio for all patients, including those in the early stages of disease.

Drug companies face bigger issues when the seeker of EA is a group of patients or an entire class of patients. Before marketing, manufacture of the drug for clinical studies is nearly an "all cost" proposition for the commercial entity; the drug cannot be marketed to cover its costs. Thus, companies generally only manufacture sufficient quantities (plus a small margin) to cover the requirements of clinical studies, rather than devote resources to manufacturing large quantities of a drug which has a <10% chance of ever making it to market (1,2). The FDA approval process begins with the filing of an investigational new drug (IND). Making the drug available to groups or classes of patients who might then deplete the supply of drug for clinical studies could compromise the very research that would more completely disclose a drug's risks and benefits; thus, it could possibly impede full market approval that would make the drug more widely available.

Companies have also expressed concern about how data from such "compassionate use" may be applied in the approval process. Patients seeking EA are usually sicker and have more advanced disease, and therefore are more likely to experience unfavorable outcomes of all types. Their experience does not necessarily apply to the entire patient population for which the drug is eventually targeted. An excess number of adverse outcomes in a compassionate use group could compromise marketing approval after clinical studies are complete.

Finally, if the drug is made available to a large enough patient base prior to marketing approval, then what patients would be willing to subject themselves to placebo-controlled trials, in which they might not receive the active therapy? Patient recruitment for clinical studies could be compromised, which could slow or even prevent the clinical trials process for full drug approval.

Such concerns are not merely theoretical, but have in fact caused significant controversy and potentially impeded the approval of some important medical treatments.

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