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TRANSLATIONAL TOOLBOX

Expanded Patient Access to Investigational New Devices

Review of Emergency and Nonemergency Expanded Use, Custom, and 3D-Printed Devices

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SUMMARY

U.S. Food and Drug Administration (FDA) approval of Class III medical devices can take from 3 to 7 years. Although this is shorter than times for drug approvals, patients with serious or life-threatening diseases and disorders may not have time to wait for device approval to access needed treatments. The FDA has a number of pathways, similar to drug approval processes, for expanded use of unapproved medical devices in patients for whom no reasonable alternative therapy is available. Additionally, the FDA regulates the manufacture and use of "custom" medical devices—those made for use by 1 specific patient. With the advent of 3-dimensional printing and bioprinting, new rules are evolving to address concerns that lines may be blurred between "custom" treatments and unregulated human experimentation. (J Am Coll Cardiol Basic Trans Science 2018;3:533–44) © 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/).

As with drugs, in the United States, the U.S. Food and Drug Administration (FDA) approval is required for the interstate transport and marketing of devices used in the treatment of human disease (1). Class I devices (e.g., bandages, hand-held surgical instruments) and Class II devices (e.g., infusion pumps, surgical drapes) present the lowest risk to patients and usually do not require clinical trials for marketing approval. Class III devices carry a significant risk of illness or injury, and usually require clinical trials. The approval process for Class III devices that have no "predicate" (i.e., a predecessor-approved device that is similar in function) and have passed preclinical bench and animal testing begins with the filing of an investigational device exemption (IDE). This exemption allows the device to be used in human trials. Further details of medical device classification and approvals, and the IDE application have been discussed in a previous review (1), and can be found at the FDA's website (2). Once a device enters the clinical testing and approval process, the average time to market is 3 to 7 years (1).

Although the time to device approval is significantly shorter than the approval process for new drugs, it is nevertheless lengthy and could prevent patients from accessing device therapy when they most need it for "life-threatening or severely debilitating disease" or "serious diseases or conditions," including "sight-threatening and limb-threatening conditions and situations involving irreversible morbidity" (3). Mechanisms have therefore evolved to allow expanded access (EA) to unapproved devices

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ABBREVIATIONS AND ACRONYMS

3D = 3-dimensional

AM = additive manufacturing

CDE = custom device exemption

CUR = compassionate use request

DBS = deep brain stimulator(s)

EA = expanded access

FDA = U.S. Food and Drug Administration

HDE = humanitarian device exemption

IDE = investigational device exemption

IRB = institutional review board

OCD = obsessive-compulsive disorder

PMA = pre-market approval

TIDE = treatment investigational device exemption

for emergency and nonemergency treatment of individuals and groups of patients.

Device approval and EA to nonapproved devices face additional issues that drug approvals do not. Drugs, once approved, may not then be chemically modified to meet individual patient requirements. Modification of many devices, such as medical implants, on the other hand, may be necessary for the treatment of a patient or patients whose needs are not met by the device in its strictly approved form. One example is an approved orthopedic implant or prosthetic device that is modified to fit the joint or limb of a patient who has special anatomy or requires it to be adapted to special use. Other examples include creation of custom vascular stents and other implants to meet unusual anatomic challenges. As the trend toward more personalized medical treatment evolves, and as evolving manufacturing methods such as 3-dimensional (3D) printing provide easier and rapid methods for device design and alteration, custom device therapy is likely to become more and more common.

This review examines the regulatory pathways by which an investigational device or implant that has not begun and/or completed clinical testing can be accessed for patients in urgent need; reviews some of the rules regarding how and when an already approved device may be modified from its strictly approved form for use in an individual patient; and explores future regulatory concerns for personalized devices created in 3D printing processes.

THE CHANGING REGULATORY LANDSCAPE

As the world's oldest consumer protection agency (4), the FDA's primary missions are to assure the efficacy and safety of both drug- and device-based medical therapies. When individual patient need is urgent, and no comparable effective therapy is available, the agency faces a challenge to provide reasonable assurances that devices are both safe and effective, while acknowledging that some patients face markedly elevated risks or disabilities from their own disease or disorder and may be willing to accept significantly higher risks in pursuit of treatment. On the other hand, FDA oversight also serves to prevent deliberate or inadvertent misuse of devices in vulnerable patient populations to further purely commercial interests.

Specific FDA pathways for EA to unapproved medical devices include a compassionate use request (CUR), custom device exemptions (CDEs), and the humanitarian device exemption (HDE). Each of these pathways has unique characteristics that are important to understand in order to determine which is the most appropriate process for use of a specific unapproved device.

Since the 1976 amendments to the Food, Drug, and Cosmetics Act, there have been multiple changes to the FDA rules and regulations regarding the acquisition by physicians of unapproved medical devices for patients facing unique, unusual, or urgent/emergent circumstances.

COMPASSIONATE USE REQUESTS

The FDA uses the term "expanded access" rather than "compassionate use" to define access to unapproved drugs or devices outside of clinical testing. EA, even if it involves a group of patients, rather than an individual patient, differs significantly from clinical studies of the device; EA is not "research" and does not have the primary purpose of generating performance, efficacy, and safety data. Overall, the number of submissions for compassionate use of devices is trending upward (**Figure 1**). Consistently, use of devices with an IDE (i.e., those in clinical trial phases) have been requested more often than those without an IDE (those not yet entered in clinical trials) (**Figure 2**). Approximately 99% of all requests for EA to devices with an IDE are granted by the FDA. Even EA to devices without an IDE are granted in 98% to 99% of cases (**Table 1**) (5,6).

When a request is made to use an unapproved device for treating a patient, the appropriate EA pathway depends on whether or not an IDE has been filed for the device, and whether the use involves treatment of a life-, limb-, or sight-threatening emergency (**Table 2**).

EMERGENCY EXPANDED USE. As with EA to investigational drugs, the FDA provides a pathway for emergency use of an unapproved device. Emergency use reports can be submitted both for those without an IDE, as well as for devices that are in clinical trials under an IDE.

Criteria for allowable emergency use are: 1) the patient has a life-threatening or serious disease or condition that needs immediate treatment; 2) no generally acceptable alternative treatment for the condition exists; and 3) because immediate use is needed in a critical situation, there is no time to obtain FDA approval for the use. The FDA now considers that limb-threatening, and sight-threatening diseases, situations involving irreversible morbidity, and those that constitute "life-threatening or serious