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TRANSLATIONAL TOOLBOX

Drugs, Devices, and the FDA: Part 2

An Overview of Approval Processes: FDA Approval of Medical Devices

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SUMMARY

As with new drugs, the U.S. Food and Drug Administration's approval process is intended to provide consumers with assurance that, once it reaches the market place, a medical device is safe and effective in its intended use. Bringing a device to market takes an average of 3 to 7 years, compared with an average of 12 years for drugs. However, there are concerns that Food and Drug Administration processes may not be sufficient to meet the assurances of safety and efficacy as intended. This second part of a 2-part series reviews the basic steps in development and Food and Drug Administration approval of medical devices, and summarizes post-marketing processes for drugs and devices. (J Am Coll Cardiol Basic Trans Science 2016;1:277–87) © 2016 The Authors. 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/).

In the early part of the 20th century, the U.S. Food and Drug Administration (FDA) was given the responsibility for ensuring both the safety and efficacy of drugs prior to marketing (1). Amendments to the Federal Food Drug and Cosmetics Act in 1976 expanded the agency's role to oversee safety in the development of medical devices (2). Whereas new drug approval takes an average of 12 years, moving new medical devices from concept to market takes an average of 3 to 7 years (3). This is the second part of a 2-part series on U.S. drug and device approval processes, and it reviews the basic steps in moving a medical device from conception to market, as well as post-market surveillance for both drugs and devices. As will be discussed, there are unique regulatory issues that are related to the device approval process.

WHAT IS A DEVICE?

Devices are regulated by the Center for Devices and Radiological Health (CDRH) at the FDA. According to the Federal Food Drug and Cosmetics Act, a device is "an instrument, apparatus, implement, machine, contrivance, implant or an in vitro reagent" that meets 3 conditions: 1) it is recognized in the official National Formulary or the U.S. Pharmacopeia; 2) it is intended for use in the diagnosis of disease or other conditions, or the cure, mitigation, treatment, or prevention of disease; or 3) it is intended to affect the structure or function of the body of humans (4). Devices cannot achieve their ends by chemical action or be dependent on metabolism (5). Some products that contain biological material are inert (e.g., acellular dermatologic fillers [6]) and can actually be considered devices. The range of objects that falls under the FDA definition of medical devices is broad, from tongue depressors and stethoscopes, to lab equipment, surgical instruments, and life-support equipment such as pacemakers, ventilators, and perfusion devices. If in doubt about whether a product is a device or a biological, the Device Determination Officer at the FDA can be of assistance (7).

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ABBREVIATIONS AND ACRONYMS

CDRH = Center for Devices and Radiological Health

eCopy = electronic copy

FDA = Food and Drug Administration

HDE = humanitarian device exemption

HUD = humanitarian use device

IDE = investigational device exemption

IRB = institutional review board

PMA = pre-market approval

PMN = pre-market notification

THE PRE-CLINICAL STAGES: PROTOTYPE DEVELOPMENT AND TESTING

Many medical devices coming to market represent successive iterations of previous devices. Development of an entirely new device typically begins with a concept by a physician or bioengineer for a solution to a medical problem. They build or arrange to have built a preliminary prototype of the device and simultaneously initiate a patent process. Preliminary bench testing is followed by animal testing, and the device enters a cycle of testing and redesign that typically takes 2 to 3 years and costs between $10 million and $20 million. Largely because of these costs, today most truly new medical devices arise out of venture-backed startup companies rather than academic medical centers (8).

REQUIREMENTS FOR CLINICAL TRIALS

Devices are classified into 3 groups by the FDA: Class I or "low risk of illness or injury" (e.g., surgical gauze [9]); Class II or "moderate risk" (e.g., suture [10]); and Class III, those which "support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential, unreasonable risk of illness or injury" (e.g., pacemakers [11]). Class I and II devices are subject to less stringent regulatory processes than Class III devices are; Class I or II device approvals are focused on registration, manufacturing, and labeling and often do not require extensive pre-clinical or clinical data. Class III devices that have only minor differences from already approved, so-called predicate devices, may be reclassified as Class I or II and are also subject to less stringent testing requirements than most Class III devices that are without predicates.

Around three-fourths of Class I devices, and a small percentage of class II devices qualify for "exempt" status, meaning there is no need for proof of safety or efficacy, nor for clinical trials (12). They also do not need to undergo the standard pre-market notification (PMN) process. Most Class II devices, however, have to demonstrate that they will perform as expected and will have to go through a PMN (aka 501[k]) clearance, which will likely not require stringent clinical evidence.

Class III devices pose significantly greater risks to patients and typically require pre-market approval (PMA), the most rigorous process required for devices by the FDA. Such devices will require clinical evidence to support the application. If a Class III device represents only minor changes from an already existing, approved device (or "predicate" device), it may not require the strict PMA process, and the sponsor can petition the FDA to reassign the device by means of a 513(g) application (13). Such devices can generally be approved by the less rigorous 501(k) process.

In general, all new devices that do not have such a predicate are automatically classified Class III by default and are required to undergo the most stringent reviews that include provision of clinical evidence and trials. However, a sponsor may also apply directly to the FDA to reclassify devices that do not have predicates to Class I or II if the device is of low to moderate risk (14). Such devices are termed "de novo" devices and are managed much like devices with predicates in a less rigorous process. A summary of devices and regulatory pathways can be seen in **Table 1**.

3 BASIC PATHWAYS TO MEDICAL DEVICE APPROVAL

There are 3 basic processes to obtain FDA marketing approval for medical devices, depending on the nature of the device and the circumstances under which approval is sought: 1) the PMA process; 2) the PMN process; and 3) the humanitarian device exemption (HDE) process.

PATHWAY 1: PRE-MARKET APPROVAL (PMA). Device manufacturers are required by federal law to notify the FDA of their intent to market a medical device at least 90 days prior to marketing. A PMA (15) is the strictest device marketing application and is required by the FDA for any new device for which there is no existing equivalent or predicate, unless such a device can be reclassified as a "de novo" device. In a PMA, a device must be shown to have sufficient scientific evidence that it is safe and effective in its intended use.

As with drug approvals, the FDA has a pre-submission process to facilitate PMA and 510(k) applications (16), and it encourages sponsors and investigators to establish early contact and collaboration with the appropriate review division in "Pre-submission" meetings, also known as "Q-sub" meetings (17). In certain cases, in collaboration with the FDA, a modified form of PMA may be allowed. One example is a "modular PMA" (18) in which sections of the application are submitted in modules as they are completed, a method usually reserved for devices in early stages of clinical studies. A current pilot program of the FDA within the Division of Clinical

Laboratory Devices is called the "streamlined" PMA (19). This PMA can be useful if the FDA has already had experience with reviewing similar devices. Whether a PMA can be "streamlined" or submitted as a modular application can be determined in the pre-submission process and may substantially reduce the time and effort to obtain approval for some devices.

Clinical evidence requirements. In general, Level I or II evidence is required to obtain FDA approval of most new class III devices (**Table 2**) (20,21). In order to conduct pre-market clinical trials with the device, investigators must first obtain an investigational device exemption (IDE), summarized in **Table 3** (17,22). Although the FDA is obliged to respond to an application within 30 days, U.S. regulations regarding device development and testing in fact typically add about 3 to 6 months to obtain FDA approval to carry out clinical studies, plus 3 to 6 months for institutional review board (IRB) approval at the clinical site. As a result, up to 75% of initial clinical testing of devices has moved outside of the United States (8).

Clinical testing typically involves a series of studies from first-in-human use, to large, multicenter prospective, randomized control trials ("pivotal" trials). Pivotal trials may require up to 1,000 subjects over a period of 1 to 2 years and follow-up for 1 year after treatment (8). The complexity of the required trials depends on the nature of the device and its proposed use.

In May 2015, the U.S. House of Representatives passed the 21st Century Cures Act (23) that, in addition to other measures, permits certain medical device approvals on the basis of observational studies and "clinical experience" rather than randomized controlled trials. The act was intended to reduce the time and expense of device approval, but it has raised serious concerns about whether the safety and efficacy of medical devices will be compromised (24,25).

Whatever the pathway of approval, early collaboration with the FDA via its pre-investigational device program is strongly advised (26); investigators can present existing data (pre-clinical data and clinical data from foreign studies) to the FDA in pre-investigational meetings and obtain suggestions from the CDRH regarding the need for additional pre-clinical data and for clinical study design prior to applying for the IDE (8). The specifics of study design can severely affect the time and cost of getting a medical device approved, and discussions with the FDA can be useful in negotiating clinical endpoints for studies.

The PMA review. PMA and PMN (aka 510[k]) applications for medical devices are reviewed by the CDRH within the FDA. Within that center are the Office of Device Evaluation and the Office of In Vitro Diagnostics and Radiological Human Health. Within these offices, the divisions are organized according to device specialties.

After receipt of a PMA, the FDA determines whether the application is sufficiently complete to begin a substantive review. The agency has 45 days to make this determination, file the application, and notify the applicant of the filing. The notification letter will include an assigned PMA reference number and the actual date of filing. The FDA then has 180 days from the date of filing for the PMA review. If the FDA refuses a PMA due to insufficiencies, it will assign a PMA reference number and notify the applicant within 45 days of the refusal regarding reasons for refusal. The applicant may supply further information, and the 180-day "clock" resets when the resubmission is filed. Alternatively, the applicant can request an informal conference with the director of the Office of Device Evaluation to review the decision within 10 working days of receipt of notification of refusal. The FDA must decide to file or refuse the submission within 5 working days of the conference.

TABLE 1 Classes of Medical Devices

	Risk	Regulatory Pathway	
Class I (e.g., gauze, toothbrushes)	Low risk of illness or injury	75% are exempt from approval	
Class II (e.g., suture, needles)	Moderate risk of illness or injury	The majority will have to go through a PMN application	
Known Class III (e.g., pacemakers, ventilators)	Significant risk of illness or injury	Has a predicate device and may be able to undergo PMN rather than the full PMA process	Does not have a predicate and generally must go through the PMA process device
New devices classified as Class III by default		If low or moderate risk, investigator may petition to have them classified as "de novo" devices, and they may be able to undergo a PMN process rather than full PMA process	

PMA = pre-market approval; PMN = pre-market notification.

TABLE 2 Levels of Evidence for a Clinical Therapeutic Study

Level I
- High-quality RCT (e.g., >80% follow-up, double-blinded) with statistically significant different or no statistically significant difference by narrow CI
- Level I RCT or systematic review and results were homogeneous

Level II
- Lesser quality RCT (<80% follow-up, not blinded, poor randomization)
- Prospective comparison studies
- Systematic review of Level II studies or of Level I studies with inconsistent results

Data from DeVries and Berlet (20).
CI = confidence interval; RCT = randomized controlled trial.

TABLE 3 IDE Process

Step 1. Investigator contacts the pre-investigational device exemptions program and requests a pre-submission meeting (these are called "pre-sub" or "Q" meetings). Time frame from submission to scheduled meeting is 75–90 days, or 21 days in cases of urgent public health need.	• Collaboration with the FDA at this stage can determine whether further clinical testing is necessary and can produce nonbinding but important suggestions regarding clinical studies and clinical design. Information about collaborative meetings and requests can be found at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073604.htm. • Submit requests for a "pre-sub" meeting to: U.S. Food and Drug Administration Centers for Devices and Radiological Health Document Control Center W066-G609 10903 New Hampshire Avenue Silver Spring, Maryland 20993-0002
Step 2. Investigator submits a complete IDE application (FDA §812.20 application). Time from submission to response: 30 days. (If no response is received 30 days after confirmation from the FDA of receipt of application, investigations can proceed)	• Currently this requires both a hardcopy of the application and an electronic copy (eCopy) on CD, DVD, or flash drive. • There is no application form. Specifics of the content and format of the IDE application, as well as checklists for content of the IDE application can be found at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046706.htm. • Submissions should be addressed to: Food and Drug Administration Center for Devices and Radiological Health Document Mail Center - WO66-G609 10903 New Hampshire Avenue Silver Spring, Maryland 20993-0002
Step 3. While waiting for response, submit application for IRB approval at the local institutions where all investigations are to be carried out.	
Step 4. What to do if a "hold" notification is received from the FDA prior to 30 days.	• Review the "hold" letter for specific reasons the application is placed on hold. • Contact the FDA to discuss how to address "hold" rationale.

FDA = Food and Drug Administration; IDE = investigational device exemption; IRB = institutional review board.

A further appeal is possible to the director of the CDRH. The director's decision is final (15).

PATHWAY 2: PRE-MARKETING NOTIFICATION (PMN): THE 510(K) APPLICATION. A PMN, also known as a 510(k) application (8,12,27), is a fast-track process for devices in which the sponsor shows that the device is substantially equivalent to an existing device that is already approved and marketed. Devices that are currently under PMA review but have not been approved cannot serve as a predicate device in a PMN for a different, new device. If the FDA determines that the device has an acceptable predicate, a PMA application is not needed, and PMN can proceed. The FDA may determine at the time of application submission that the proposed predicate does not qualify and refuse the 501(k) application, and then a full PMA will be required. The FDA has provided a decision-making algorithm for determining substantive equivalence of a proposed predicate device (28). PMN must be submitted to the FDA at least 90 days prior to anticipated marketing.

The PMN process has been criticized as introducing additional risks to consumers, because the assumption that the device is "equivalent" to another already marketed device may be unsound. One example is the Pinnacle metal-on-metal acetabular cup liner marketed by DePuy Orthopaedics (Raynham, Massachusetts) was "fast tracked" by the FDA based on its nearly identical predicate, the Ultima system (DePuy Orthopaedics), but had to be discontinued in 2013 due to unacceptable rates of patient-adverse reactions (12).

Another problem with the PMN process is that "serial predicates" can occur—in other words, a new device can be approved using as its predicate another device that was itself approved based upon yet another, different predicate. This means that a current device can be approved based on a PMA that occurred several "generations" prior to the current one in a series of similar devices. Decades can pass between the current device in question and the original PMA and clinical evidence supporting it. In 2011, the Institute of Medicine recommended eliminating the PMN approval process, based on this specific concern (29,30). In addition, the Institute of Medicine recommended enhancing the post-marketing surveillance system for medical devices. The Institute of Medicine did not provide specific plans for such changes, and the report was met by protests from manufacturers that the changes would slow technological innovation, harm patients, and cost manufacturing jobs (3).

Additional criticisms of the PMN process include worries that it incentivizes manufacturers to develop new devices that are only slight improvements over their forerunners rather than true innovations, but for which they can nevertheless charge a premium price as a "new" device (30,31). One example of this occurred in the development of the Cerecyte coil marketed by Micrus Endovascular (San Jose, California) for treatment of intracranial aneurysms. The manufacturer was able to charge a premium for the device without having to provide prospective evidence that the product was superior to other coils currently on the market. Later, prospective studies demonstrated efficacy, but nonsuperiority compared with existing devices. The result was that overall costs to patients increased, but for a nonsuperior product (3).

Finally, the fast-track process has the potential to slow active enrollment of human subjects in clinical studies. Manufacturers can receive reimbursement

for devices in use without having to produce class I evidence regarding efficacy. Therefore, motivation to complete such studies may be diminished (32).

De novo devices. Most new devices that do not have predicates are automatically classified as Class III and must undergo the full PMA process, including the submission of Class I or II evidence of clinical efficacy. However, sponsors can petition to reclassify low- or moderate-risk devices that do not have predicates (and would not ordinarily qualify for 510(k) applications) as "de novo" devices. If a device is classified as de novo it can undergo the PMN process rather than the more rigorous PMA. Devices approved as de novo devices can then serve as predicates for other devices (33).

The PMN review process. In a PMN (27), the sponsor supplies 2 copies of the application (1 of which must be an electronic copy or "eCopy") plus a user fee to the CDRH's Document Control Center. A summary of 2016 user fees for applications can be found in **Table 4** (34,35). If the user fee or eCopy are not included in the application, a hold will be placed on the application and a hold letter sent to the submitter within 7 days. The submitter then has 180 days to resolve issues regarding the fee and eCopy. If both fee and eCopy are received, the submitter will receive an acknowledgment letter identifying the date of receipt of the application and assigning the application a unique control number, commonly referred to as a "510K number," or "K number." This letter does not constitute a clearance for marketing, but is merely a confirmation that a review process has begun.

Once it is assigned a "K number," the submission is then routed to the appropriate CDRH division based on device type and medical specialty involved. Within the division, the submission is assigned a lead reviewer, who conducts an "acceptance review" to determine that all essential elements of the application are complete, so that a substantive review can begin. The acceptance review is completed, and the submitter is notified of the results within 15 days of receipt of an application, eCopy, and user fee. When the application is moved to substantive review, the lead reviewer is also identified to the submitter.

Within 15 days of notification of substantive review, FDA reviewers must answer some basic questions to the lead reviewer, including whether the product or a component thereof is a device, whether the submission has been made to the appropriate center, whether the device is of a classification that is eligible for a 510(k) submission, and other details. Full details of the inquiries can be found in the "Refuse to Accept Policy for 510(k)s" section on the FDA website (16).

TABLE 4 Medical Device User Fees per Type of Application for 2016

	Standard Fee	Small Business Fee
510(k) or PMN	$5,228	$2,614
513(g) application for device reclassification	$3,529	$1,765
PMA	$261,388	$65,347

Abbreviations as in Table 1.

After basic questions are answered, the FDA must respond with an approval or denial within 60 days of the receipt of a complete 501(k) PMN (i.e., within 45 days of acceptance for substantive review) (16).

PATHWAY 3: THE HUMANITARIAN DEVICE EXEMPTION (HDE). A humanitarian use device (HUD) is one that is expected to treat or diagnose conditions that affect fewer than 4,000 individuals in the United States annually. HDE are handled through the Office of Orphan Products Development at the FDA. The use of an HUD requires approval and supervision by a local IRB in addition to approval by the FDA (36). The application for an HDE is similar to that for a PMA, except that scientific evidence of efficacy is *not* required, under the rationale that it could take years to even find enough subjects to provide sufficient power in order for a clinical study to attain statistical significance. The device sponsor is only required to demonstrate that there is a probable benefit to health, and that the probable benefit outweighs the risk of injury or illness caused by the device. In other words, the HDE requires demonstration of device-relative *safety*, but not device *efficacy*.

To protect particularly vulnerable patient cohorts from manufacturers who might hope to profit from devices with unproven efficacy, the price the manufacturer can charge for such devices is limited to covering manufacturing fees, research and development expenses, and other closely defined costs. Any device costing more than $250 must submit a report from an independent certified accountant attesting to the excess cost and reasons for it (36). Some exceptions for that rule are provided for devices used in pediatric populations.

An approved HDE allows use of the HUD, but only at institutions that have established local IRB to oversee clinical testing of devices, and only after local IRB approval. The device labeling must state that it is a humanitarian device, and that although authorized for use by federal law, the effectiveness of the device for the specific indication has not been demonstrated (36).

The HDE review process. Obtaining an HDE involves 2 steps: obtaining designation of the device as

TABLE 5 Emergency or Expanded Use of Investigational Devices

	Time Frame	Criteria	Application Process	Time to Approval/ Treatment
Emergency use	Immediate need	• Life-threatening or serious condition • No alternative treatment • No time to get FDA approval	Submit IDE report to the FDA of an emergency use within 5 days of use, giving details of the case and patient protection measures followed	Approval is post hoc
Emergency research	Prior to initiating a clinical trial involving emergency interventions	• Emergency research in which the human subject of the research is in a life-threatening situation and it is not feasible to get informed consent	Regular IDE submission process: in addition to IRB approval, a physician not involved in the project must review and approve	Regular IDE approval timeline
Compassionate use	During clinical trial of the device; physician wants to treat a patient who does not meet trial inclusion criteria	• Patient with a serious condition or disease • No alternative treatment • Patient does not otherwise qualify for inclusion in the clinical study, but the physician believes they may benefit • Usually for use in a single patient, but can sometimes be for a small group	FDA approval required before treatment: sponsor submits an IDE supplement requesting compassionate use under section §812.35(a)	Regular IDE approval timeline
Treatment use	During clinical trial of the device; data suggest the device is effective, and the investigator wants to expand the number of enrollees to include other patients with life-threatening or serious disease	• Life-threatening or serious disease • No alternative • Controlled clinical trial • Sponsor actively pursuing market approval	FDA approval required prior to treatment. Investigator submits a treatment IDE application under section §812.36	Treatment use may begin 30 days after the FDA receives the submission
Continued access	After the clinical trial has concluded: FDA may allow enrollees to continue to receive treatment while the approval process is underway	• Public health need or • Preliminary results suggest the device will be effective, and no safety concerns have been identified for the proposed indication	Investigator submits an IDE supplement requesting continued access or an extended investigations permit	Treatment has presumably begun during the trial and continues after

Use of an investigational device in humans is generally restricted to approved clinical studies in accordance with an approved protocol. The FDA has mechanisms for using unapproved, investigational devices to save the life of a patient, or for patients suffering from serious diseases for which no alternative therapy exists.

Abbreviations as in Table 3.

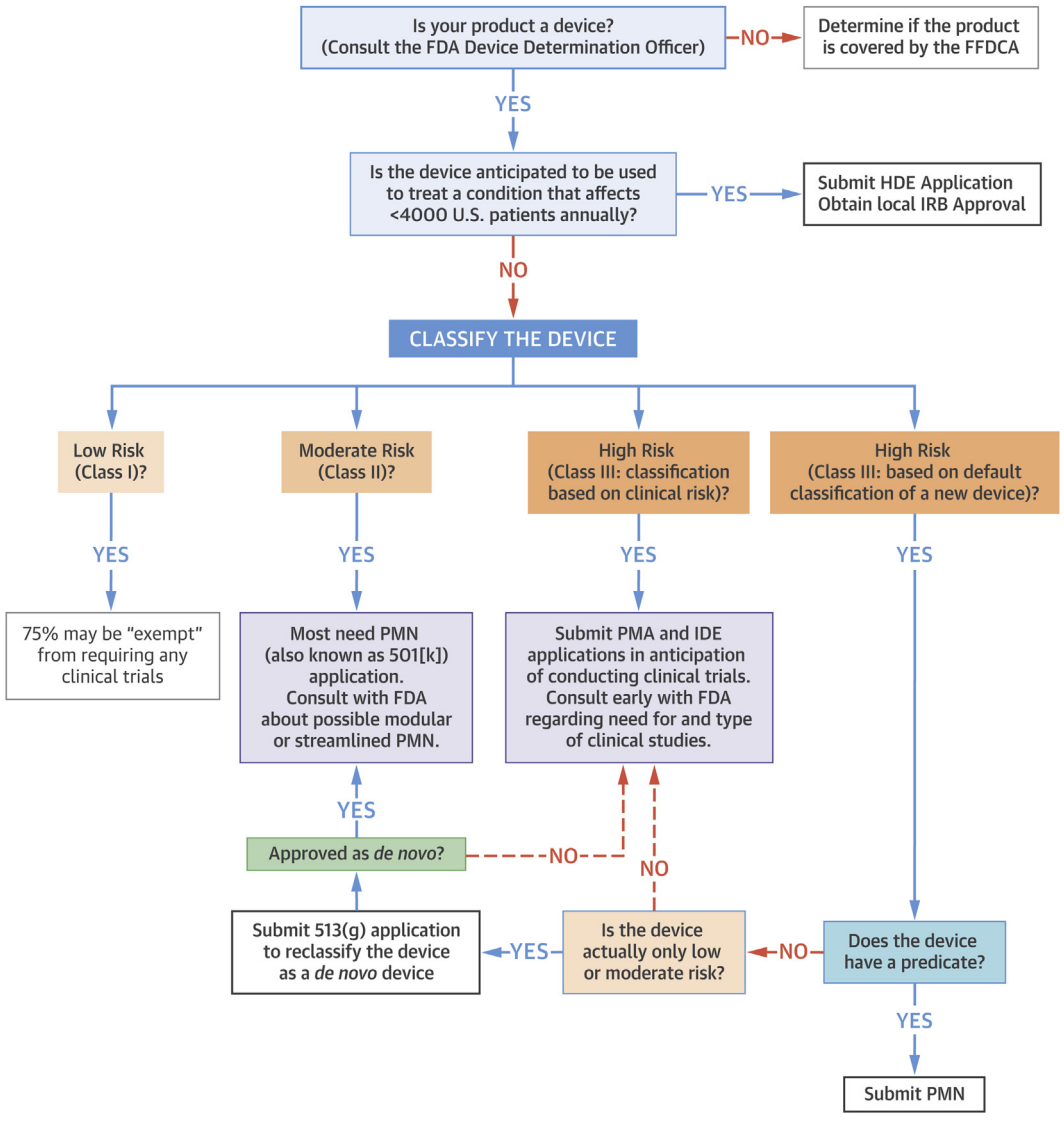
an HUD, and then submitting an application for HDE. The FDA will respond within 45 days of submission of an application for designation of a device as an HUD in 1 of 3 ways: 1) approve the device as an HUD; 2) ask for further information; and 3) refuse the designation. Refusals are often based on findings that the condition for which the HUD is being sought affects >4,000 people annually in the United States. If the device is designated an HUD by the FDA, the applicant can submit an application for HDE. The FDA has 30 days for an acceptance review to determine that the application is complete enough for a substantive review, and then within 45 days of that notification (75 review days total) will respond with a notification of approval, disapproval, or nonapproval (meaning more information is needed) (37).

EMERGENCY AND EXPANDED APPROVALS FOR USE OF AN INVESTIGATIONAL DEVICE (IDE). As with investigational drugs, the FDA has provisions for allowing the use of an investigational (unapproved) device to save the life of a patient, or to treat a patient for which there is no alternative therapy available. Within the application process are 5 potential ways in which health care providers can obtain approval to legally use an investigational device for such patients before it has been approved. These are summarized in Table 5 (38,39).

OVERVIEW OF HOW TO OBTAIN FDA APPROVAL FOR A MEDICAL DEVICE

STEP 1: CLASSIFY THE DEVICE. The first step for the sponsor (after determining that the product is a device) is to classify the device (as Class I, II, or III) (Central Illustration). Even though the FDA will do this during the review of the pre-market submission, it is nevertheless important for the sponsor to do so as well, because that will determine which submission

CENTRAL ILLUSTRATION **FDA Medical Device Approval Pathways***



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*Early consultation with Food and Drug Administration (FDA) through pre-submission meetings in strongly encouraged; the FDA can help determine which pathway and applications are needed, as well as determine whether clinical trials are necessary. FFDCA = Federal Food, Drug, and Cosmetics Act; HDE = human device exemption; IDE = investigational device exemption; IRB = Institutional Review Board; PMA = pre-market approval; PMN = pre-market notification.

path is appropriate for the device. To facilitate this, the FDA offers a searchable database with device classifications (7). Classification of the device will also determine the regulatory control during and after the marketing process, important issues for the sponsor to consider.

If the device is an entirely new device, determine whether it has a predicate or could be reclassified a "de novo" device of low to moderate risk that does not have a predicate. The sponsor can petition the FDA for reclassification of the device and attempt approval along the 501(k) application pathway.

STEP 2: SELECT THE APPROPRIATE PRE-MARKET SUBMISSION PATHWAY. Class I devices and many Class II devices, as well as Class III devices with

predicates can usually forego PMA and proceed with a 510(k) application. A PMA is required for most Class III devices, with valid Level I or II scientific evidence providing reasonable assurance of safety and efficacy. If the device is Class III and intended to benefit fewer than 4,000 patients annually in the United States, the investigator should proceed with a request for designation of the device as an HUD. After receiving designation as an HUD, the investigator should prepare an HDE application to exempt the device from having to provide stringent evidence of efficacy.

STEP 3: IF THE DEVICE REQUIRES A FULL PMA. Clinical trials will be required and the investigator should prepare an IDE application. The PMA can proceed after obtaining sufficient Level I and II clinical evidence.

STEP 4: PREPARE THE APPROPRIATE APPLICATION. The FDA provides resources at their website to direct sponsors regarding the necessary information, depending on whether the application is a PMA, a 501(k) PMN, or an HDE. In general, the applicant must supply information about device indications and function, basic scientific concepts, summary of all adverse safety and efficacy information, procedures to control risks, alternative procedures and treatments to the device, summary of pre-clinical and (in the case of PMA, HDE, and some 501[k]) clinical trial data, and a bibliography of references. Pre-submission contact with the FDA for feedback on medical device approval is highly encouraged.

Prior to initiating any clinical study of the device for the purpose of a PMA, HDE, or 501(k) application, the investigator must obtain IDE from the FDA as well as local IRB approval.

STEP 5: SEND THE SUBMISSION TO THE FDA. Recall that a user fee and eCopy on a compact disc, digital video disc, or flash drive are required for acceptance reviews. Within 15 days of receipt of a submission, eCopy, and user fee, the FDA will complete an administrative acceptance review and respond. If there are issues regarding the user fee, eCopy, or information in the packet, the review may result in a "hold," and the sponsor will be notified. The sponsor then has 180 days to resolve issues. If there are no issues (or after issues are resolved) the FDA will assign a lead reviewer and notify the applicant of acceptance for a complete review. FDA communications with the applicant will occur while the device is under review to increase efficiency of the review process.

The FDA assigns the times at which interactions will occur as: 1) within 60 days of receipt of a complete submission for 510(k) (i.e., 45 days after acceptance for complete review); and 2) within 90 days of the filing date for PMA (i.e., within 75 days of acceptance for complete review).

STEP 6: REGISTER THE ESTABLISHMENT AND LIST THE DEVICE. Once FDA approval is given, the sponsor must register the business that will produce and distribute the device within the United States and "list" their device (40).

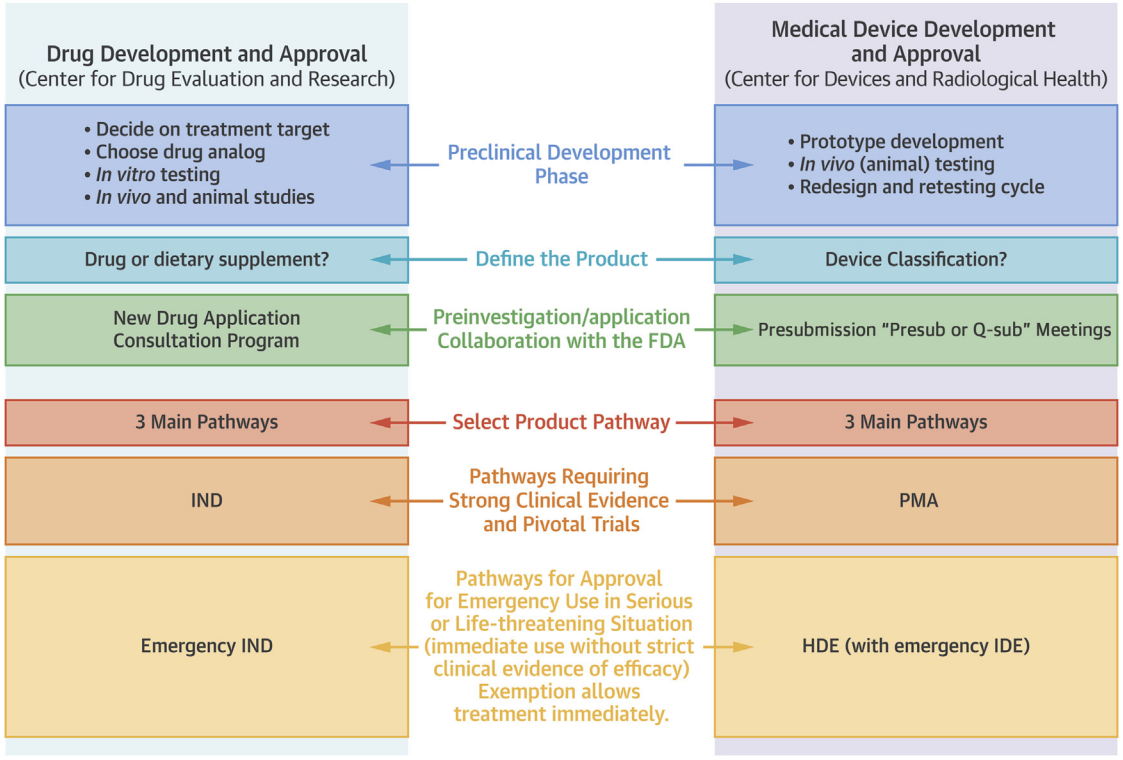
POST-APPROVAL FOLLOW-UP FOR DRUGS AND DEVICES

DRUGS: PHASE IV STUDIES AND POST-MARKETING REGULATORY STEPS. Following approval and marketing of a drug, phase IV ("post-marketing") studies may be undertaken to test the drug in additional patient populations (e.g., pediatric patients), in new delivery modes (e.g., timed-release capsules or transdermal patches), or for treatment of a different medical condition. These trials must meet the same standards as phase III clinical trials. Additional phase IV data may include patient surveys regarding drug side effects and other patient-reported issues (41).

The FDA's post-market regulatory procedures require that manufacturers report all serious and unexpected adverse reactions to the FDA. In addition, mechanisms allow for physicians and patients to report issues. The Office of Surveillance and Epidemiology identifies drug safety concerns and recommends actions to improve product safety, by monitoring the relevant publications, conducting studies using computer databases, and watching for signals of safety problems of marketed drugs by reviewing adverse event reports (42).

OFF-LABEL USE OF DRUGS. Once approved by the FDA, the agency is empowered to regulate the marketing of a drug, but not the practice of medicine. This means that a drug company may only advertise and market a drug for the specific purpose approved by the FDA. Marketing or advertising a drug for another purpose requires an application for a "labeling change" through the FDA (43). An FDA-approved drug can legally be used by a qualified physician in ways other than those approved by the FDA, so long as the physician is well-informed, bases the new use of the drug on sound medical evidence, and maintains records of its use. According to the FDA, "Use of a marketed product in this manner *when the intent is the 'practice of medicine'* does not require the submission of an Investigational New Drug Application (IND), Investigational Device Exemption (IDE) or review by an institutional review board" (43). Local institutions can, however establish policies that

FIGURE 1 Similar Processes in Drug and Device Approval



HDE = human device exemption; IDE = investigational device exemption; IND = investigational new drug; PMA = pre-market approval.

require that such "off-label" use be approved by an IRB, although it is uncommon for them to do so.

DEVICES: POST-MARKET REGULATIONS AND PROCESSES. After a device goes to market, federal regulations require hospitals, health professionals, and other users of medical devices to report patient incidents involving the device, both to the manufacturer and to the FDA if the incident results in serious patient injury, death, or other patient-adverse experiences (44). Hospitals are additionally required to track use of certain devices if failure of the device could result in a serious adverse health outcome. The FDA may require manufacturers to put post-marketing surveillance plans in place (45) and to submit a post-marketing surveillance report if the device meets any of the following criteria (46):

- its failure would be reasonably likely to have serious adverse health consequences;
- it is expected to have significant use in pediatric populations;
- it is intended to be implanted in the body for more than one year; or
- it is intended to be a life-sustaining or life-supporting device used outside a device user facility.

At times, a PMA or HDE (and other new device protocols) may be approved by the FDA conditional on the future completion of certain clinical studies. These studies are then tracked by the CDRH to ensure completion and continued safety and efficacy of the device. A recent study suggests, however, that such conditional approvals may be problematic; the investigators found that as long as 5 years after approval, only 18% of devices that had been approved by the FDA conditional on the completion of further clinical studies in the post-market period had actually undergone such studies (47). Another 18% had not been subjected to any post-market trials. While some such trials would take more than 3 to 5 years to complete and therefore may be pending, the investigators questioned whether they in fact will ever be completed.

Banned devices. In extreme cases, the FDA may decide to ban a device from the Federal Register if it

determines, on the basis of all available data and information, and after consulting with the appropriate classification panel, that a device intended for human use presents deception (such as adulteration or mislabeling) or risk of illness or injury that cannot be corrected by a change in labeling (48).

SUMMARY

Drug and device approval pathways share common characteristics (**Figure 1**). Each has special presubmission opportunities for collaboration with the FDA. Each has 3 main pathways to approval. For each there is a main pathway requiring significant clinical evidence of efficacy and safety (the Investigational New Drug Application and the PMA, respectively), and a pathway for emergency use (the emergency investigational new drug and the Emergency Use notification, respectively). Deciding which path to initiate is only the first of a series of challenges that face the investigator. Early and regular communication with the FDA is encouraged to avoid pitfalls and problems that may waste time and resources.

Streamlining processes for drug and device approval is an important goal, but doing so without compromising the FDA's ability to ensure the safety and efficacy of new drugs and devices for patients will remain a continuing challenge.

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