

How medical devices are approved in the US

In the US, the Food and Drug Administration's Center for Devices and Radiological Health (CDRH) is responsible for regulating medical devices. The Office for Device Evaluation within CDRH is responsible for the regulatory review and approval of medical device applications, and they provide guidance at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm>.

CDRH outlines the three main steps in marketing a medical device.

1. Ensure the product is a device. The product may be a drug or biological product such that it falls under other divisions within the Food and Drug Administration (FDA).
2. Determine how FDA may classify the device. The classification will determine the level of regulatory control and the process of marketing approval.
3. Develop the data required to submit a marketing application and obtain FDA clearance to market the product.

Medical devices are categorized as class I, II or III. The regulatory requirements increase in stringency as one moves from class I to class III. The class of device will determine the submission requirements required for FDA to provide clearance for commercialization. Device classification depends on the intended use of the device as well as the indications for use. In addition, the classification is risk-based, meaning that the level of risk the device poses to the patient or user is a major factor in determining its class.

Class I: This group covers devices subject to general controls. Most class I devices are *exempt devices*.* Some devices require a 510(k) submission (see below). Examples of class I devices include crutches, elastic bandages and bedpans.

Class II: This group covers devices subject to general and special controls. Most class II devices are approved under a 510(k) pre-market notification submission, but some are exempt devices. Examples of class II devices include sutures, inflatable blood pressure cuffs and condoms.

Class III: This group covers devices subject to general controls, special controls and pre-market clearance. Most class III devices are approved under a pre-market approval (PMA) procedure. Examples of class III devices include drug-eluting coronary stents, cardiac ablation catheters, artificial hearts and breast implants.

**Exempt devices* are those specifically exempted by regulation, and pre-amendment devices. A pre-amendment device is one that was marketed prior to 1976 and has not been modified, and the FDA has not published a regulation requiring a PMA.

Device classifications can be found on the FDA's website by searching its Product Classification Database (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm>). New types of devices may not be found in this database. If the device is a high-risk device (i.e., it supports or sustains human life, is of substantial importance in preventing impairment of human health, or presents a potential, unreasonable risk of illness or injury) and has been found to be not substantially equivalent to a class I, II or III device, then it will require a PMA.

Class I/II exempt devices–Notification procedure

A class I device must be suitable for its intended use. Manufacturers of class I/II exempt devices are required to notify the FDA rather than submit an application for marketing approval. The device must be labelled appropriately

and the manufacturer must have its establishment registration and device listing forms on file with the FDA. A marketing application is not required but the manufacturer must be able to demonstrate it manufactures according to good manufacturing practices (GMP). The quality-assurance program must be adequate to ensure the labelling meets GMP requirements. In addition, manufacturers must have adequate procedures in place for safety documentation and to record any patient or user complaints, adverse events or other safety issues.

510(k) pre-market notification

The 510(k) procedure is used for class II devices that are subject to the general controls of class I devices but also require special controls. Special controls may include labelling requirements, mandatory performance standards, or post-marketing surveillance. A 510(k) application must demonstrate that the device is substantially equivalent to one marketed in the US before May 1976, or determined by the FDA to be substantially equivalent. A manufacturer must compare its device to one or more marketed devices and demonstrate the claims of substantial equivalency. The legally marketed device against which the comparison is made is called the “predicate” device. Substantial equivalence means the new device is at least as safe and effective as the predicate.

A device will be assessed as substantially equivalent to a predicate if it:

- has the same intended use *and* the same technological characteristics
- OR
- has the same intended use and has different technological characteristics and the information submitted to the FDA does not raise new questions of safety and effectiveness, and the manufacturer demonstrates that the device is at least as safe and effective as the predicate

The FDA aims to review a 510(k) submission within 90 days. The manufacturer may not market the new device until it receives a letter of substantial equivalence from the FDA.

510(k) de novo submissions

The 510(k) de novo submission is for a novel “first-of-a-kind” device for which no predicate device exists. Prior to May 1976, any device not in commercial distribution was automatically classified as class III, requiring a PMA submission. The latest regulations provide a new mechanism for classifying new devices for which there are no predicates. The process cannot be used to reclassify an existing class III device.

The application process involves a discussion between the manufacturer and the FDA (via teleconference or pre-IDE meeting [see below]) of the possibility of a de novo 510(k) submission. The application is submitted as a de novo 510(k) similar to a traditional 510(k). The data are considered by the FDA and the appropriateness is determined on a case-by-case basis. The 510(k) application results in a letter that declares the product is not substantially equivalent (due to a lack of a predicate device). The manufacturer then has 30 days to send a petition to reclassify the device. The petition must include a risk/benefit analysis and a discussion of the proposed controls to ensure the safety and effectiveness of the device. Once the FDA receives the classification request, it has 60 days to review the petition, evaluate the risk, identify applicable controls, write a special controls guidance document, classify the device, write the approval order, and write the Federal Register notice of availability of the special controls guidance document. Once the FDA signs the approval order, the new device can be marketed 30 days after the final approval order is published in the Federal Register.

An example of a device for which a de novo 510(k) submission may be appropriate is a lower-risk *in vitro* diagnostic test that has no predicate.

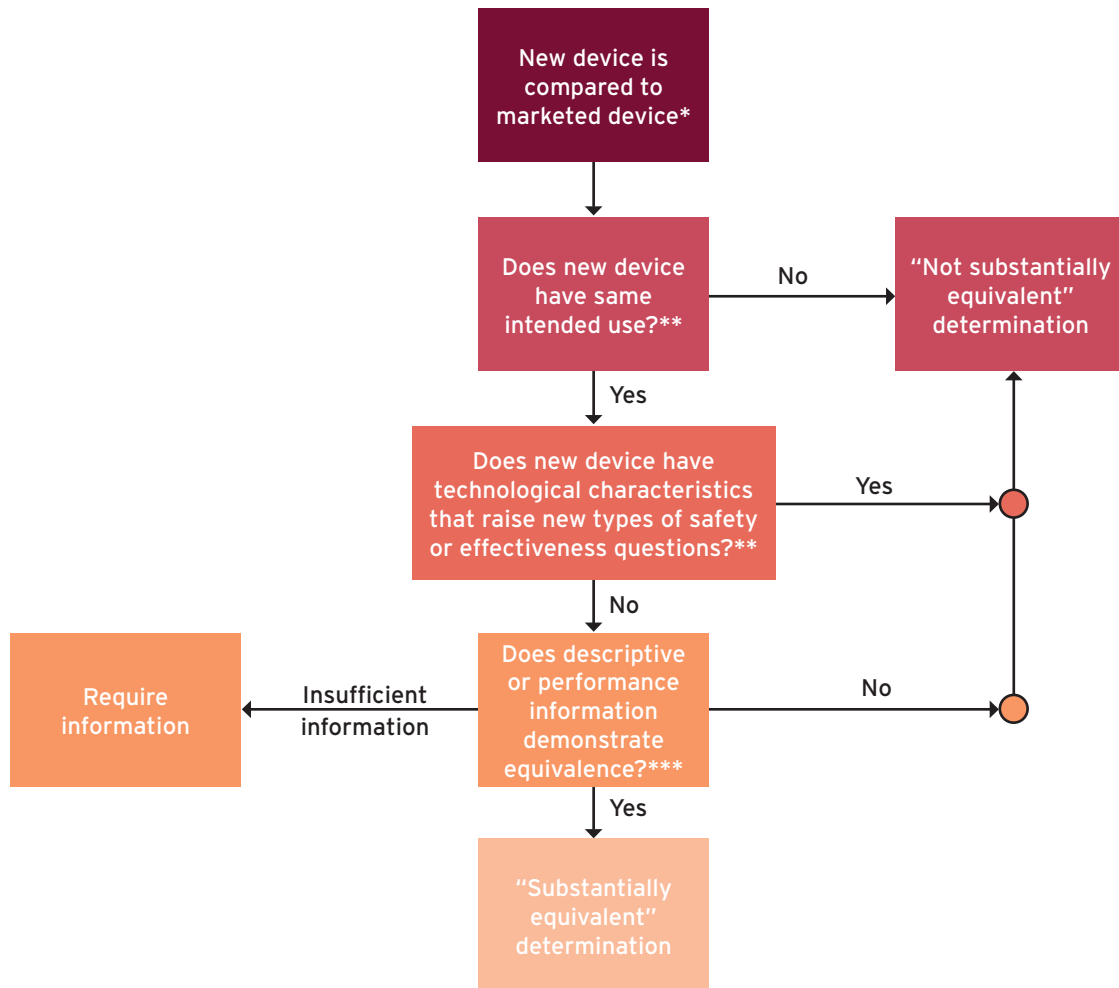
510(k) review process

After CDRH receives a 510(k) application the file is sent to the appropriate reviewing division. It is then screened for acceptability. This screening process is an administrative review and does not comprise a scientific review. The FDA targets 30 days for the screening review. If the file is considered administratively incomplete, a *Refuse to Accept* letter is sent to the manufacturer detailing the omissions and inadequacies. The 510(k) is placed on hold until the deficiencies have been rectified. The sponsor has 30 days to submit the required information or request an extension of up to 180 days.

Once the application is accepted for review, it undergoes a scientific review. If the reviewer needs additional information, the sponsor may be contacted by telephone for minor requests, or by letter for major requests, in which case the submission is placed on hold until the sponsor responds. Usually, a written request for additional information requires a response within 30 days, or the sponsor will need to request an extension explaining the reason why and the amount of extra time needed.

At the completion of the review, the FDA issues a letter either granting marketing authorization or stating the reasons for denial. A 510(k) application is not considered “approved” by the FDA, but rather, the FDA letter states that the manufacturer’s device is substantially equivalent to another marketed device and is now cleared for sale.

Exhibit 1: 510(k) "Substantial equivalence" decision-making process (overview)



* 510(k) submissions compare new devices to marketed devices. FDA requests additional information if the relationship between marketed and "predicate" (pre-amendments or reclassified post-amendments) device is unclear.

** This decision is normally based on descriptive information alone, but limited testing information is sometimes required.

*** Data may be in the 510(k), other 510(k)s, the Center's classification files, or the literature.

Source:

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM081394.pdf>

Pre-market approval

Pre-market approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of class III medical devices. Class III devices are high-risk devices that pose a significant risk of illness or injury, or are devices found not to be substantially equivalent to class I or II devices. The PMA process requires the submission of clinical data to support the safety and efficacy of the medical device. All clinical studies must be carried out under an approved Investigational Device Exemption (see below).

The FDA targets 180 days to review a PMA, but, in reality, the timeframe is usually much longer. The PMA process is similar to the New Drug Application process in that an advisory committee meeting may be called to discuss the new device.

A PMA contains two main technical sections:

1. **Non-clinical laboratory studies**—includes information on microbiology, toxicology, immunology, biocompatibility, stress, wear, shelf-life and other laboratory and animal tests
2. **Clinical investigations section**—includes study protocols, safety and effectiveness data, adverse reactions and complications, device failures and replacements, patient information, patient complaints, tabulations of data from all individual subjects, and results of statistical analyses

Each PMA submission undergoes a screening process. An administrative review checks to ensure all the required elements of the PMA application are present. If any are missing, FDA can refuse to file the PMA and it will be returned to the sponsor. Key decisions made by the FDA during the screening review include:

1. Is the PMA sufficiently organized to permit substantive review?
2. Is the PMA sufficiently complete to permit substantive review?
3. From the standpoint of the administrative review, do the data submitted in the PMA appear to constitute valid scientific evidence?
4. Were the data from the clinical studies collected and analyzed per the protocols?
5. Were the non-clinical and clinical data collected on the final design of the device (i.e., the device intended to be marketed)?
6. Were the patient population and endpoints selected appropriately?
7. Does the PMA address the key non-clinical and clinical issues identified by the FDA prior to submitting the PMA application? Or, has the applicant provided a detailed scientific or clinical justification for the alternate approach?

After passing the administrative review, the PMA undergoes a scientific review. The sponsor may request to meet with the FDA at a “Day 100” meeting to discuss the status of the application. This request must be made when the PMA is filed, or within 70 days of filing. At this meeting, the sponsor and the FDA may discuss:

- any issues and possible actions
- an action plan with estimated dates of completion
- estimated timetables from the FDA for review completion
- identification of the need for panel involvement
- possible pre-market and post-market requirements

The FDA may refer the PMA to an advisory committee of independent experts for review and recommendation. This referral commonly occurs with “first-of-a-kind” devices.

The outcome of the PMA review can be one of the following:

- **Approval order:** The PMA is approved and the manufacturer can sell the device.
- **Approvable letter:** The FDA review is complete and minor deficiencies need to be resolved (these are identified in the letter), or the final approval is subject to a satisfactory inspection by the FDA of the manufacturing facilities.
- **Major deficiency letter:** The PMA lacks significant information necessary for the FDA to complete its review and the application needs amendment.
- **Not approvable letter:** The FDA review is complete and the application cannot be approved due to significant deficiencies (outlined in the letter). The manufacturer can submit a complete response to a not-approvable letter which restarts the FDA review clock.
- **Denial order:** The FDA has decided not to approve the application. All deficiencies are identified in the letter. The review is considered complete and the denial order marks the end of the FDA process.¹

Investigational Device Exemption

Clinical studies done on investigational devices that are considered “significant risk” must be conducted under an Investigational Device Exemption (IDE). A “significant-risk” device is one that presents a potential for serious risk to the health, safety or welfare of a subject. The IDE process is similar to a clinical trial application for a new drug. The IDE permits the collection of safety and effectiveness data to support the PMA or 510(k) submissions. All clinical investigations must have an approved IDE before a study begins. The IDE must also be approved by the appropriate institutional review board and be conducted according to Good Clinical Practice (GCP).

Similar to a clinical trial application, after 30 days the IDE is considered accepted by the FDA unless the sponsor has heard earlier that it has been approved or not approved. If not approved, the sponsor has the opportunity to respond to the deficiencies in a file.

Devices of non-significant risk are those that do not pose a significant risk to humans. Prior to initiation, these studies only require the approval of an institutional review board, and an IDE is not needed.

Meetings with the FDA

Similar to the drug division at the FDA, the medical device division has established advisory committees of experts to provide independent, professional expertise and technical assistance. At the conclusion of a review of a PMA, the FDA may schedule an Advisory Committee meeting to discuss the safety and effectiveness of a new medical device.

In addition to formal Advisory Committee meetings, FDA staff are available to discuss clinical investigations and marketing applications for medical devices. At the clinical investigation stage, a pre-IDE meeting may be warranted to discuss, either formally or informally, how best to develop the device. At informal guidance meetings, sponsors are encouraged to meet with the Office of Device Evaluation (ODE; a division of the FDA) to discuss pre-clinical data and the proposed clinical investigation before they submit an IDE. There are no binding recommendations that stem from informal guidance meetings. These are opportunities for a sponsor to meet with staff from the reviewing division to discuss the proposed clinical plan and available pre-clinical data.

Formal guidance meetings take place after a sponsor makes a written request for a meeting to reach an agreement with the FDA regarding the FDA's review of an investigational plan, including the clinical protocol. The written request should include the following:

- a detailed description of the device
- a detailed description of the proposed conditions of use
- a proposed clinical protocol
- information regarding the expected performance of the device

If an agreement is reached between the sponsor and the FDA, the terms should be put in writing. The agreement then becomes binding.

Sponsors may also wish to conduct pre-PMA meetings or pre-PMA filing meetings. A pre-PMA meeting is usually held to review the broad outline of a clinical trial design. The FDA will determine whether clinical studies will be needed to demonstrate the device is safe and effective for its proposed use. A pre-PMA filing meeting is held to discuss the contents of a PMA and familiarize FDA staff with the forthcoming application.

¹US Department of Health and Human Services, Food and Drug Administration. (2008, June 30). *FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Goals*. Retrieved February 25, 2010, from <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089733.htm>

FDA review timelines

Exhibit 2: Summary of device classifications and target approval times in the US

	Class I	Class II*	Class III
Type of application	Exempt	510(k)	PMA
Target review time	Registration	90 days	180 days

* Some class II devices are deemed exempt.

Source: US Food and Drug Administration, <http://www.fda.gov/>

For more information on the approval process for medical devices in the US, visit <http://www.fda.gov/medicaldevices>.