FDA Clearance of Medical Devices

LEARNING OBJECTIVES
1. Explain the FDA’s role in ensuring medical devices cleared for market in the United States are safe for use
2. Describe how the FDA defines and classifies medical devices
3. Review FDA requirements for registering and listing medical devices
4. Discuss how to submit or update a premarket notification 510(k) application or a premarket approval application
5. State the FDA’s definition of “labeling”

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OBJECTIVE 1: EXPLAIN THE FDA’S ROLE IN ENSURING MEDICAL DEVICES CLEARED FOR MARKET IN THE UNITED STATES ARE SAFE FOR USE
The FDA protects the public’s health in numerous ways. For example, it assures the safety, efficacy and security of human and veterinary drugs, biological products, the nation’s food supply, cosmetics, products that emit radiation, and medical devices.

The FDA regulates all aspects of the manufacture of a wide range of medical devices – from simple ones, such as tongue depressors, thermometers and surgical gloves, to very complex ones, such as heart pacemakers and robotic surgery instruments. Other covered items include those for dental use, surgical implants, and prosthetics.

Medical devices are regulated under the FDA’s Center for Devices and Radiological Health (CDRH). The beginning of strong medical device oversight began with the enactment of the 1976 Medical Device Amendments. This legislation gave the FDA various enforcement mechanisms, including the ability to ban devices, revoke premarket approval (PMA), and detain a manufacturer’s shipment of products. The legislation also created advisory panels that enabled FDA personnel to seek advice from external experts to assist in the regulatory process.

At this time, medical devices were divided into three classes, based on risk: Class I, Class II and Class III. All classes are subject to general controls administered by the FDA, including registration, listing, quality system regulations (QSRs), good manufacturing practices (GMPs), labeling, and reporting of adverse events caused by medical devices (medical device reporting).

OBJECTIVE 2: DESCRIBE HOW THE FDA DEFINES AND CLASSIFIES MEDICAL DEVICES
The FDA considers a medical device to be an instrument, apparatus, implement, machine, contrivance, implant, in vitro diagnostic product (reagents, instru-
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SOME DEFINITIONS

- **PREMARKET APPROVAL (PMA)** – FDA approval granted to manufacturers of some new devices to demonstrate the devices are safe and effective.

- **QUALITY SYSTEM REGULATIONS (QSRs)** – A quality system is the organizational structure, responsibilities, procedures, processes, and resources for implementing quality management.

- **GOOD MANUFACTURING PRACTICES (GMPs)** - The regulations that govern the manufacture and testing of medical devices and other medical products.

**In summary:** A manufacturer receives FDA premarket approval (PMA) of new medical devices by, in part, detailing how the manufacturing process will meet quality system regulations (QSRs) that incorporate the use of good manufacturing practices (GMPs).

WHAT IS THE DIFFERENCE BETWEEN A 510(K) AND A PMA?

- **510(k)** - Manufacturers must submit a 510(k) for relatively low-risk devices to the FDA for approval before the devices can be marketed. FDA approval means the devices are at least as safe and effective as similar predicate devices that existed prior to May 28, 1976, and that do not require a PMA.

- **PMA** - Manufacturers must submit for FDA approval a PMA for new and usually relatively high-risk devices before the devices can be marketed. A PMA is needed when there is no predicate device against which a manufacturer can compare a new device for safety and effectiveness.

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- **“Recognized in the official National Formulary, the United States Pharmacopeia, or any supplement to them;**

- **Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man or other animals; or**

- **Intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals, and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.”**

As suggested above, the FDA’s definition of a medical device includes almost everything from a bandage to a complex surgical robot. The FDA further classifies medical devices in terms of the risk presented to a person or animal when the device is used.

Class I devices (example: tongue blades) are deemed to present the lowest risk to a person when they are used. These devices are only subject to general controls, such as registration and listing. Most, but not all, must adhere to QSR and GMP requirements. Most Class I devices are not subject to PMAs and do not require a 510(k) application to be submitted before they can be marketed in the US. Note: a 510(k) is a premarket submission to FDA that demonstrates the device to be marketed is at least as safe and effective as (is substantially equivalent to) a legally marketed device that does not require a PMA.

Class II devices (example: hand-held medical instruments) have the potential to cause more harm to a person than a Class I device and, therefore, require increased regulatory controls to ensure they are safe and effective for use. Class II devices are also subject to general controls: registration, listing and adherence to the QSRs and GMPs. Some Class II devices are not subject to a PMA but, if it is required, a 510(k) application is needed. Many Class II devices are also subject to special device-specific controls that address performance standards, after-market surveillance, patient registries, special labeling requirements, pre-market data requirements, and guidelines.

Class III medical devices (example: artificial heart) are those that present the highest level of risk when used. They are subject to general and specific controls, including adherence to QSRs and GMPs; however, because of the degree of risk associated with Class III medical devices, the FDA has determined that general and special controls alone are not adequate to ensure the safety and effectiveness of these devices. Therefore, the FDA also requires a PMA to provide sufficient valid scientific evidence to ensure the covered device will be safe and effective for its intended use. A Class III device that is denied a PMA is considered adulterated and cannot be marketed in the US.

**OBJECTIVE 3: REVIEW FDA REQUIREMENTS FOR REGISTERING AND LISTING MEDICAL DEVICES**

Companies involved in the production and commercial distribution of medical devices in the US are required to register with the FDA and pay a $3,646 fee per establishment (2015 cost) annually. Most must also list the devices that will be...
EXAMPLES OF SPECIAL CONTROLS FOR CLASS II MEDICAL DEVICES

Many Class II devices are subject to special device-specific controls in addition to general controls. For example, the FDA recognizes several additional standards for surgical gowns including:

- AAMI/ANSI PB70:2012 Liquid barrier performance and classification of protective apparel and drapes intended for use in health care facilities

manufactured, sold or distributed by the company in the US and other parts of the world.

If a device requires a PMA or 510(k) notification, the PMA number must be provided at the time of annual registration. The registration and listing information provides the FDA with location and product data useful during a public health emergency.

Several types of companies must register and list their devices with the FDA:

- Manufacturers: Those using chemical, physical, biological, or other procedures to make items meeting the definition of “device” in Section 201(h) of the Federal Food Drug, and Cosmetic (FD&C) Act. Accessories and components are considered medical devices in their own right when sold directly to the end user.
- Contract manufacturers: Those constructing a finished device to another company's specifications.
- Contract sterilizers: Those providing a sterilization service for another establishment's devices.
- Repackagers: Those who package into different containers (excluding shipping containers) finished devices from bulk or repackage devices made by a manufacturer.
- Relabelers: Those who change the labeling content from that supplied by the original manufacturer for distribution under their (the relabeler's) own name.
- Specification developers: Those who develop specifications for a device distributed under their own name, but who perform no manufacturing. This includes those who, in addition to developing specifications, also arrange for the manufacturing of devices labeled with another establishment's name by a contract manufacturer.
- Reprocessors of single-use devices: Those who perform remanufacturing operations on a single-use device.
- Remanufacturers: Those who process, condition, renovate, repackage, restore, or do anything else to a finished device that significantly changes the finished device's performance, safety specifications, or intended use.
- US manufacturers of “export only” devices: Those who manufacture medical devices not sold in the US that are manufactured solely for export to foreign countries.

OBJECTIVE 4: DISCUSS HOW TO SUBMIT OR UPDATE A PREMARKET NOTIFICATION 510(K) APPLICATION OR A PREMARKET APPROVAL APPLICATION

Unless exempted by the FDA, all medical devices require either a premarket notification 510(k) or PMA before a company can commercially distribute them in the US. Most Class III devices will need to be approved through the PMA application process, although some can be approved with a Class III 510(k).

MORE ABOUT PREMARKET APPROVAL (PMA)

Premarket Approval (PMA) is the FDA's most stringent type of medical device marketing application. The PMA process is a multi-step process that requires a minimum of 180 days to complete; usually longer times are needed.

A device subject to a PMA frequently involves new concepts that are not comparable to previously-cleared medical devices. If a Class I, II or III device is found to not be substantially equivalent, it must be approved through the PMA application process before it can be sold in the US.

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510(K) APPLICATION

A 510(k) application requires proving a device is substantially equivalent to one or more “predicate” devices legally marketed before the 1976 medical device amendments (see above). Note: “Substantially equivalent” means a device is at least as safe and effective as the predicate device; it does not necessarily mean a new device is identical to the predicate device.
Substantial equivalence can also be requested by claiming a product is equivalent to one that has been declared substantially equivalent to a device through the 510(k) process. Until the company receives an FDA order that the device is substantially equivalent, the device cannot be marketed in the US.

For a device to be considered substantially equivalent, it must:

- Have the same intended use as the predicate device;
- Have the same technological characteristics as the predicate device, or have the same intended use as the predicate device; and
- Demonstrate that the device is at least as safe and effective as the legally marketed device.

Four categories of companies must submit a 510(k) to bring a product to market if the product is not subject to a PMA:

- Domestic manufacturers who manufacture a device according to their own specifications and intend to market it in the US. *Note: Contract manufacturers who manufacture a device in accordance with someone else’s directions are not required to submit a 510(k).*
- Specification developers who develop the specification for a device and then contract with a manufacturer to make the product.
- Repackagers or relabelers who make labeling changes or whose operations significantly affect the device. Changes that could warrant submission of a 510(k) include changes to manuals by the repackager or relabeler, and altering the intended use of a device. Other changes can relate to deleting or adding warnings and including contradictions, such as changing the intended use of a sterilizer to include sterilization of devices that were not part of the original 510(k). *Note: Most repackagers or relabelers do not need to submit a 510(k).*
- Foreign manufacturers/exporters or US representatives of foreign manufacturers/exporters wanting to introduce a device to the US market.

Companies must submit a 510(k) to introduce a device into commercial distribution by that company for the first time. Submission must be made at least 90 days before offering the device for sale. If a company proposes a different intended use for a device for which they already have a 510(k), a new 510(k) will likely be needed.

The 510(k) regulation specifically requires a new submission for any major change to the device or its use. For example, changing a device from prescription to over-the-counter use will require a new 510(k). Whenever a change or modification is made to a device that could significantly affect its safety or effectiveness, a new 510(k) application must be submitted. The 510(k) holder must decide if the change is such that a significant impact on the device’s safety or effectiveness will occur. These changes must be made according to QSRs and must be recorded in the device’s master record and change control procedures.

Submission of a 510(k) is not required in certain circumstances. For example, companies who sell unfinished products or components to another company who will use the product in producing the final device do not need to file a 510(k). However, if a component is sold to the end user for replacement parts then a 510(k) submission is needed.

When a device is not marketed or commercially distributed, a 510(k) is not required. An example occurs when a company reprocesses surgical linen and instruments for a hospital-owned co-op and only distributes the devices to member hospitals. However, if the company desires to sell these devices to parties other than co-op members, a 510(k) is required. Then all FDA requirements must be met, including registration, listing, 510(k) submission, and adherence to the QSRs and GMPs.

A device documented to be in legal commercial distribution before the 1976 medical device amendment date does not need a 510(k) submission, unless the device is significantly modified. These devices can only be marketed by the original owner of the device.

Certain Class I and Class II devices are exempt from the 510(k) process, and a list can be found on the FDA website. Companies that manufacture these devices must still follow general controls, including facility registration, device listing, and following the QSRs, GMPs and medical device reporting requirements.

**PMA APPLICATION**

You have learned that the PMA process involves using scientific and regulatory evidence to show a medical device is safe and effective for its intended use.

Some Class III devices are considered pre-amendment, and they might require a Class III 510(k) instead of a PMA. Device product classifications can be found by searching the Product Classification Database on the FDA website.

Good science and science writing are keys to the PMA application process. PMA applications that lack essential elements and/or that are poorly written will be refused. Devices receiving a PMA that are modified require submission of a new PMA, and the modified device cannot be sold until the new PMA has been approved.

**OBJECTIVE 5: STATE THE FDA’S DEFINITION OF “LABELING”**

The FDA defines a “label” as a “display of written, printed or graphic matter upon the immediate container of any article…” In contrast, “labeling” is defined as “all labels and other written printed, or graphic matter 1) upon any article or any of its containers or wrappers, or 2) ac-
companying such article. Note: The term, “companying” is broadly interpreted to mean more than a physical presence on the device and extends to posters, booklets, brochures, and instructions providing in-depth information about the device. Advertising is generally considered to be part of the “labeling” for a device.

General device labeling requirements include:

- The name and address of the company manufacturing or distributing the device
- The intended use of the device
- Adequate usage directions that allow a layperson to safely use the device for its intended use or purpose(s),
- No false or misleading statements. Note: When this occurs, the device is considered misbranded.
- All labeling must be in English, unless the device will be distributed solely in a US territory in which English is not the predominant language.
- Labels must remain in place and be legible for the normal time a device could be in use.

Since labeling is part of the device’s master record, any labeling changes must be made under a formal change control process. Labeling changes that modify how a device is used or reprocessed might require submission of a new 510(k) or PMA if the change is considered significant, with the potential to impact the device’s safety and effectiveness.

Certain types of devices have specific labeling requirements, such as warning, caution and use-related statements, and other information designated for the specific type of device. For example, devices sold sterile or that will be user-sterilized have specific labeling requirements.

Devices that are partially sterile must be clearly labeled to identify sterile and non-sterile areas. For example, IV tubing may only have a sterile fluid path, and this must be clearly stated with a limiting statement, so the user knows the tubing cannot be used on a sterile field. Reusable devices to be sterilized require labeling that details the steps needed to clean and sterilize the device, the type of sterilization method used and sterilization parameters.

IN CONCLUSION

The FDA regulates companies who manufacture medical devices according to the degree of risk associated with using a specific device. The FDA also ensures that all medical devices are safe and effective for their intended use, and this effort begins with registration and listing requirements. Premarket notification is then used to ensure that medical devices sold in the US are safe and effective for their intended use. Companies are inspected to ensure compliance with all FDA requirements, including premarket notification, QSRs and GMPs.

REFERENCES


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OBJECTIVE 1
1. Strong oversight of medical devices by the FDA began with the passage of the:
   a. 1976 Medical Device Amendments
   b. 1978 CGMP Requirements for Medical Devices
   c. 1990 Safe Medical Devices Act
   d. 1997 Global Harmonization of Medical Devices

2. FDA divides medical devices into classes based on the:
   a. Complexity of the manufacturing process
   b. Type of premarket notification needed
   c. Degree of risk associated with use of the device
   d. Type of controls needed to manufacture the device

OBJECTIVE 2
3. Most Class I devices are subject to approval through the PMA application process.
   a. True
   b. False

4. Many Class II medical devices are subject to FDA clearance through:
   a. Special device-specific controls
   b. Quality System Regulations
   c. Current Good Manufacturing Practices
   d. All the above

5. Devices subject to PMA frequently involve devices that:
   a. Present a low risk of causing harm to patients when used
   b. Are exempt from the 510(k) clearance process
   c. Are substantially equivalent to previously-cleared medical devices
   d. Are not comparable to any previously-cleared medical devices

OBJECTIVE 3
6. Who must register with the FDA?
   a. Relabelers
   b. Shipping container repackagers
   c. Physicians
   d. a and b above

7. Reprocessors of single-use devices are not required to register and list devices with the FDA.
   a. True
   b. False

8. Registration and listing provides the FDA with what information:
   a. Device safety information
   b. Product complaint files
   c. Process validation files
   d. Location and product information

9. How often must companies involved in the production and distribution of medical devices in the US register with the FDA?
   a. Semi-annually
   b. Annually
   c. Every two years
   d. Every 3 years

OBJECTIVE 4
10. FDA requires premarket notification of:
    a. All medical devices not specifically listed as exempt
    b. Class I medical devices
    c. Class II medical devices
    d. Class III medical devices

11. A 510(k) application requires proving that a device is:
    a. Manufactured for use only in the United States
    b. Manufactured according to the QSR
    c. Substantially equivalent to one or more predicate medical devices
    d. Manufactured in accordance with CGMP requirements

12. Devices that have received a PMA that are subsequently modified require submission of a new PMA.
    a. True
    b. False

13. A new 510(k) or PMA must be submitted when a manufacturer makes a change or modification to a device that could significantly affect the device’s safety or effectiveness.
    a. True
    b. False

14. A PMA approval indicates that the FDA has determined that there is:
    a. Substantial equivalence between the device and a low risk predicate device
    b. Substantial equivalence between the device and any legally marketed device
    c. Sufficient scientific evidence to show that a device will accomplish its intended purpose
    d. Sufficient scientific evidence to assure that the device is safe and effective for its intended use

OBJECTIVE 5
15. What is the FDA’s definition of “labeling?”
    a. A display of written printed or graphic matter upon the container of any article
    b. All labels and other written, printed, or graphic matter on any article or its containers or wrappers
    c. The components required to create a Device Master Record
    d. The written instructions needed to use the device