MEETING HIGHLIGHTS

Medical Design and Manufacturing East Conference and Exhibition 2009

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More than 3,000 people, including 50 representatives from academia and industry, attended a conference in New York City from June 8 to 11, 2009. Participants from the FDA reviewed the requirements and procedures for approval of medical devices. FDA discussants included William Sutton, Deputy Director of the Center for Devices and Radiological Health (CDRH); Marjorie Shulman, Consumer Safety Officer; Julie “Brandi” Stuart, Consumer Safety Officer, CDRH; and Michael Marcarelli, Director of Bioresearch Monitoring, Office of Compliance, CDRH.

INTRODUCTION

Medical devices are an integral part of modern medicine today and offer patients a quality of health care that had not been available before gifted scientists, engineers, and physicians created these items. The use of a medical device can afford patients the opportunity to maintain a healthier lifestyle than could have been attained otherwise.

The heart of device regulation is a three-tiered classification system under which products approved before 1976 were categorized by the risk they posed to patients. The higher the number for the device class, the more complex the regulatory process.

Advances in medical technology are occurring at unprecedented speed, creating many improvements in our country’s approach to health care. Cardiac medicine is just one therapeutic area that has been virtually transformed by innovations in medical technology. Breakthroughs such as coronary stents, implantable defibrillators, and minimally invasive bypass surgery have helped to reduce death rates from heart disease by 40% since 1980. DNA-based tests and other advances in diagnostics are saving lives because of detection of cancer at an earlier stage, when the disease is usually more treatable.

Although medical devices have changed the way in which physicians treat patients, there have been unanticipated problems. For example, some devices have been recalled. The Thoratec TLC II Portable Ventricular Assist Device (VAD) Driver, a mechanical pump that helps a weak heart pump blood through the body, is sometimes called a “bridge to transplant” because it can help a patient survive until heart transplantation can be performed. The device was recalled because of the possibility that the VAD support for the patient’s circulatory system might fail. The VAD driver could stop as a result of early wearing-out of the compressor motor, and the compressor motor could stop without warning. If the motor fails, blood flow to and from the patient’s heart would be inadequate.

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DEFINITION

A device is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or another similar or related article. It may also include any component, part, or accessory that is:

• recognized in the official National Formulary or the U.S. Pharmacopeia or in any supplement to these.
• intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans or animals.
• intended to affect the structure or any bodily function in humans or animals and that does not achieve its primary intended purpose via a chemical and that does not need to be metabolized to achieve its primary purpose.

BACKGROUND

In 1938, when Congress passed the Federal Food, Drug, and Cosmetic Act (FFDCA), medical devices were simple instruments such as stethoscopes and scalpels. Any defects in the device, if present, were readily apparent. Since that time, the number and complexity of medical devices has increased greatly, ranging from simple heating pads to more complicated equipment such as pacemakers, intrauterine devices, fetal stents, and kidney dialysis machines.

Although some of the earliest devices, such as bandages, have retained their same basic form and function, their complexity has increased exponentially over the past 61 years. Patient care has improved dramatically as a result of these changes. Since 1976, the FDA has regulated the approval of medical devices in terms of their safety and efficacy.

Pre-amendment devices, introduced before May 28, 1976, are “grandfathered” for purposes of premarket review. These serve as “predicate” devices for post-amendment devices; they can remain on the market unless legal action is taken to remove them or unless they are Class III and the FDA requires premarket approval applications (PMAs) for them.

Post-amendment devices were introduced into commercial distribution after May 28, 1976; a premarket review is required.
for these devices. If a new company wishes to market the same type of device as one that is grandfathered, it must submit a Premarket Notification, or a 510(k), showing “substantial equivalence.” The company must then receive clearance.

**CLASSIFICATION**

Three regulatory classes are recognized under Section 513(a)(2) of the FFDCA. These classes are based on controls, risk, and the reasonable assurance of the device’s safety and effectiveness.

**Regulatory Device Classes**

**Class I.** These devices do not pose an unreasonable risk of patient illness or injury. They are regulated only via general controls, such as general labeling requirements, record-keeping, premarket notification, and good manufacturing practices (GMPs). These controls apply to all Class I devices as well as to devices of Classes II and III. The FDA does not assess Class I products individually, and the safety and effectiveness of the individual product do not need to be established before it is marketed. Most Class I devices are exempt from a Premarket Notification 510(k). Examples include tongue depressors and crutches.

**Class II.** These devices present a greater risk of harm and are subject to additional regulation in the form of special controls, which the FDA may establish. Although regulation may be more stringent with Class II devices, the FDA does not evaluate these products individually. Generally, this class includes higher-technology products that do not by themselves maintain life, such as cardiac monitors, tampons, and oxygen masks. Special controls include performance standards, guidance documents, postmarketing surveillance, and patient registries. Most Class II devices require a Premarket Notification 510(k).

**Class III.** It might not be evident whether general or special controls are sufficient to provide reasonable assurance of the safety and effectiveness of Class III devices. These devices are used to support or sustain human life; they might be of substantial importance in preventing impairment of health, or they might present a potentially unreasonable risk of illness or injury. Technically, all Class III products are subject to a PMA process in which a manufacturer must establish the safety and efficacy of the device before it is marketed. Examples include implantable devices (stents and heart valves) as well as products used within the body (angioplasty catheters and coils for embolization).

**Regulatory Class Types of Premarket Submission**

The regulatory class determines the type of premarket submission required:

- A Class I device can be exempt from premarket review unless a 510(k) approval is required by regulation.
- A Class II 510(k) approval is required unless the device is exempt from 510(k) requirements by regulation.
- A Class III PMA is required if an applicant must demonstrate the safety and effectiveness of its device without relying on a grandfathered or predicate device. Each PMA must stand on its own. A 510(k) approval must show equivalence in terms of its intended use and technology.

**510(k) DEVICES**

A 510(k) is the largest FDA premarket program addressing a great diversity of product types. Fifty percent of all devices reach the market as “510(k) exempt,” and 3,000 to 4,000 510(k) devices are submitted for approval each year. These applications are supported by user fees that have been negotiated with the industry. Most 510(k) devices are in Class II.

Almost all devices carrying a significant risk that are approved via the 510(k) route are implants and life-sustaining and life-supporting devices. Approximately 8% of 510(k) devices are reviewed by third parties. A 510(k) is not a PMA. A legally marketed 510(k) must establish equivalence to a legally marketed (predicate) device that does not require a PMA. Examples include a pre-amendment device that the FDA considers to be substantially equivalent, a reclassified device, or a device classified by a petition de novo.

A new device is considered to be substantially equivalent (SE) to a predicate device:

- if it has the same intended use.
- if it has the same technological characteristics.
- if it has different technological characteristics but does not raise new questions of safety and effectiveness.
- if it is as safe and effective as the predicate device.

**Predicate Device**

A predicate device is one that was legally marketed prior to May 28, 1976, or has been reclassified from Class III to Class II or I to which the submitter of a new device claims substantial equivalence. The manufacturer must ensure that adequate, valid scientific evidence exists and must provide reasonable assurance of the device’s safety and effectiveness to the FDA. The indication for a 510(k) device may differ from that of the predicate device as long as both devices have the same intended use.

**Indications for Use**

Intended use refers to the purpose or intent of the persons legally responsible for the labeling of devices. An indication for use is a general description of the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended.

**Safety and Effectiveness**

The terms safety and effectiveness refer to the possible benefits to health versus probable injury or illness from use of the device. The safety and effectiveness of a 510(k) device may differ from that of a predicate device as long the risk–benefit ratio is equivalent for both devices. Technological differences can include modifications in design, materials, or energy sources.

A 510(k) submission is required:

- when a company first introduces a device to the market.
A modification may refer to a change in the indication, use, design, materials, chemical composition, energy source, or manufacturing process of a device that significantly affects its safety and effectiveness. A company can buy a 510(k) device and may have the legal right to commercially distribute a device with the specifications on file with the FDA.

Since 1976, the FDA has reviewed 510(k) submissions for more than 146,000 devices, or an average of 3,000 to 4,000 devices per year. Each submission shows incremental changes over its predicates, and the FDA provides appropriate regulatory and scientific evaluation to increase access to new technologies while at the same time protecting the public health.

The number of 510(k) submissions that include clinical data is increasing. Examples include embolic protection devices, daily-wear contact lenses, vascular devices for coronary artery bypass, glaucoma shunts, barbed sutures, and image-guided bronchoscopes. For all of these submissions, more in-depth reviews, as well as occasional panel input, are required. Of all 510(k) submissions, 10% to 15% contain clinical data that are collected under an Investigational Device Exemption.

**DEVICES NEEDING PREMARKETING APPROVALS**

A premarket approval (PMA) by the FDA is required to ensure the safety and effectiveness of Class III devices. The device undergoes a scientific review to determine the risks and benefits compared with substantial equivalence.

Thirty to 50 PMAs are submitted to the FDA each year. A Premarket Notification for a PMA and a 510(k) device is needed for new devices and transitional Class III devices (e.g., gauze, adhesive tape, tampons, dialysis fluid, denture cushions). Devices that need or will eventually need PMA preamendments are Class III devices and substantially equivalent post-amendment Class III devices.

Safety and effectiveness data that are obtained rely on valid scientific evidence only. A device that is in final form for sale to an end-user is subject to 510(k) requirements.

**Enforcement Discretion**

Sometimes the FDA decides not to enforce a regulatory requirement; if so, the device is then exempt from 510(k) requirements by regulation or statute. Unlike an exemption from a regulation, enforcement discretion may apply to only one aspect of a regulatory requirement.

A firm may not both manufacture and distribute a device without its own 510(k) approval.

**INVESTIGATIONAL DEVICES: FDA OVERSIGHT**

An investigational device is any health care product that does not achieve its primary intended purpose by chemical action or metabolism. A FDA-approved Investigational Device Exemption (IDE) permits a device to be shipped for conducting investigations. A significant risk (SR) study of a device presents a potential for serious risk to the health, safety, or welfare of a participant. A nonsignificant risk (NSR) study of a device does not meet the definition of an SR device and does not present a potential for serious risk to the health, safety, or welfare of participants. An IDE is used to gather clinical performance data for research and development or to support a PMA or a 510(k). To meet the criteria of an IDE, the device:

- must be noninvasive.
- must not require an invasive sampling procedure that presents a significant risk.
- must not, by design or intention, introduce energy into a person.
- must not be used as a diagnostic procedure without confirmation of the diagnosis by an established product or procedure.

In another exemption category, the device must not be used to determine the safety and effectiveness of Class II devices and must not put patients at risk. It must be limited to consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution.

Informed consent for IDEs must meet requirements of the institutional review board’s (IRB’s) policies and procedures. There must be no claims of safety or superiority over other devices. The IDE must be “investigational” and not yet approved by the FDA. The FDA must have access to patient’s medical records, and the participant must be informed that the IDE is experimental and that benefits are unproven.

Any unanticipated adverse effect to participants from the device must be reported to the IRB no later than 10 working days after the clinical investigator learns of the event.

**DEVICES FOR HUMANITARIAN USE**

A Humanitarian Use Device (HUD) is intended to be used in fewer than 4,000 individual in the U.S. per year. A HUD Exemption (HDE) is an FDA approval that allows a physician to use the device in clinical treatment or in a clinical investigation. The physician must use the device only in accordance with its labeling and in the population designated by the FDA approval. Only the holder of the HDE agreement with the FDA may use the HUD. The clinical investigator:

- must promptly report any unanticipated problems to the FDA and the IRB.
- must promptly notify the FDA or the IRB if there is evidence that the device contributed to the death or serious injury of a patient.
- must report any FDA actions to the IRB.
- must report any modifications to the device or its clinical use to the IRB.
- must notify the patient of any new information concerning the use and safety of the device.

The emergency use of an FDA-regulated investigational device (HUD) with a human subject is indicated for an immediate life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval. If it is anticipated that a device might be used in an emergency situation and if there is enough time, the physician should provide sufficient information to the IRB so that it can determine whether the anticipated use...
meets the FDA regulatory requirements. However, emergency use usually takes place when there is no time for an IRB review. The physician should obtain (1) agreement from the IRB chairperson if time permits, (2) informed consent from the patient or legal representative if possible, (3) an independent assessment by an uninvolved physician, and (4) institutional clearance. After an IDE is granted, the FDA should notify the holder of the IDE or HDE. The use of the IDE must be reported to the IRB within five working days, and information on its use and on the patient’s condition should be reported to the holder of the IDE or HDE, who then makes a report to the FDA.

THE 510(k) REVIEW

During a 510(k) device review, the FDA determines whether a proposed device is substantially equivalent (SE) or not substantially equivalent (NSE) to a Class I or II device that has already been approved.

Substantial equivalence. If the device is declared to be substantially equivalent, an official FDA letter is issued to the submitter stating that the FDA has determined that the device is substantially equivalent to a legally marketed device. The device can then be sold in the U.S., subject to FDA requirements. This decision marks the end of the FDA's review. The reported review time is the number of cumulative FDA days for all review cycles from the date the device is received to the date on which the letter indicating substantial equivalence is issued. The time frame is usually within 90 FDA days from the date on which the device is received (if it is the first action on the submission) or within 90 cumulative FDA days (if the determination of substantial equivalence is a second or a later action).

Nonsubstantial equivalence. If a device is judged to be nonsubstantially equivalent, the FDA issues a letter to the submitter stating that it has determined that the device may not be sold in the U.S. In general, the FDA issues a letter indicating nonsubstantial equivalence:

• if no predicate device exists.
• if the device has a new intended use compared with that for the predicate device.
• if the device’s technological characteristics raise new questions of safety and effectiveness other than those for the predicate device.
• if the device’s indications for use or its technological characteristics differ from those of the predicate device.
• if performance data do not show that the device is as safe and as effective as a legally marketed device.

A determination that a device is nonsubstantially equivalent marks the end of the FDA's review. The reported review time is the number of cumulative FDA days for all review cycles from the date the device is received to the date on which the letter indicating nonsubstantial equivalence is issued.

POST-APPROVAL STUDIES

The Post-Approval Studies (PAS) Program of the Center for Devices and Radiological Health (CDRH) encompasses design, tracking, oversight, and review for studies mandated as a condition of approval of a PMA or an HDE application. The program helps to ensure that well-designed post-approval studies are conducted effectively and efficiently and in the least burdensome manner. CDRH has established an automated, internal tracking system that identifies the reporting status of active post-approval studies ordered since January 1, 2005, based on timelines incorporated in study protocols and agreed on by the CDRH and applicants. This system represents the CDRH's effort to ensure that all commitments to post-approval studies are fulfilled in a timely manner.

DEVICE RECALLS

A device can be recalled after weeks, months, or years of general use in the market in a large patient population. A recall often represents a problem of quality (or a lack thereof) in manufacturing or an unexpected safety problem.

FEES

The standard 510(k) fee for the FDA's review of a medical device is $3,693. The fee for a PMA for a small business with less than $30 million in gross receipts is $200,725. The PMA fee for a small business with less than $100 million in gross receipts is $500,181.

CONCLUSION

Rapid advances in device development and biomedical imaging have greatly enhanced the ability of physicians to treat and to diagnose a variety of diseases. This increased ability often leads to improved outcomes for patients. However, these improvements—combined with (1) a rise in entrepreneurial activity by physicians, (2) the practice of defensive medicine in order to thwart malpractice suits, and (3) the power of patients who demand more effective treatment—have led to sharp increases in the volume of medical devices and imaging services and the expenditures for them. Medical device development is often technology-driven, the “user” may have no voice, and, as in all industries, a cost–benefit ratio must be demonstrated. High-profile cases of medical errors may prove enough to improve standards related to patient requirements.

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