INTRODUCTION

In order to promote the appropriate use of new or emerging endoscopic technologies, the ASGE Technology Committee has developed a series of status evaluation papers. By this process relevant information about these technologies may be presented to practicing physicians for the education and care of their patients. In many cases, data from randomized controlled trials is lacking and only preliminary clinical studies are available. Practitioners should continue to monitor the medical literature for subsequent data about the efficacy, safety and socioeconomic aspects of the technologies.

BACKGROUND

Federal law mandates the Food and Drug Administration (FDA) to ensure that marketed medical devices are safe and effective. The perception by physicians and industry is that this process can be frustratingly long. The Food and Drug Administration Modernization Act of 1997 (FDAMA) was enacted by Congress to address these problems. This report is an update of the 1996 Device Evaluation and the Food and Drug Administration Process Status Evaluation Report.¹

CHRONOLOGY AND LAWS GOVERNING FDA’S JURISDICTION

The basic framework governing the regulation of medical devices is established in the Medical Device Amendments to the Federal Food, Drug and Cosmetic (FFD&C) Act. The Medical Device Amendments were enacted on May 28, 1976 and separated the regulation of medical devices from the regulation of foods and drugs.² The FFD&C Act was again amended with respect to the regulation of medical devices by the Safe Medical Devices Act (SMDA) of 1990 and the Medical Device Amendments of 1992.³ Congress amended the FFD&C again with the Food and Drug Administration Modernization Act of 1997 (FDAMA).⁴ This new model has improved manufacturing design controls and has speeded up the review process while reducing the cost to the FDA, clinical investigators, medical device manufacturers, and subsequently consumers. With respect to medical devices, the FDA is directed to focus its resources on the regulation of those devices that pose the greatest risk to the public and those that offer the most significant benefits. The FDA must base its decisions on clearly defined criteria and provide for appropriate interaction with the regulated industry. The new legislation assumes that enhanced collaboration between the FDA and regulated industry will accelerate the introduction of safe and effective devices to the U.S. Specific changes include:

Practice of Medicine:

Synopsis: Nothing in the FDAMA limits or interferes with the authority of a physician to prescribe or administer any legally marketed device to treat any disease or condition if done within a legitimate health care practitioner-patient relationship. However, the FDA retains its current authority to restrict the sale, distribution, or labeling of devices and to prohibit the promotion of unproven uses.

Dissemination of Information on New Uses:

Synopsis: The FDAMA abolishes the long-standing prohibition on dissemination by manufacturers of
information about unproven uses of drugs and medical devices. The act allows a firm to disseminate peer-reviewed journal articles about an off-label indication of its product, provided the company commits itself to file, within a specified time frame, a supplemental application based on appropriate research to establish the safety and effectiveness of the unapproved use. While the act reduces or simplifies many regulatory obligations of manufacturers, it does not lower the standards by which medical products are introduced into the market place. In the area of medical devices, the act specifies that FDA may keep out of the market products whose manufacturing processes are so deficient that they could present a serious health hazard. The law also gives the agency authority to take appropriate action if the nature of the device is likely to be used for a potentially harmful unlabeled use.

Device Standards:

Synopsis: The FDAMA added a system for recognizing national and international standards in product reviews. The use of recognized standards is a significant step toward global harmonization of medical devices. The FDA may, through publication in the Federal Register, recognize all or part of an appropriate standard established by a nationally or internationally recognized standards in a Declaration of Conformity, which can be used to satisfy a premarket submission requirement [PMA or 510(k)] or other requirement under the FFD&C Act to which such a standard applies. The FDA can request supportive data. The FDA may reject the declaration if information supplied does not demonstrate that the device conforms to the standard, or if the standard is inapplicable. The FDA may withdraw such recognition of a standard, through publication of a notice in the Federal Register, if the Agency determines that the standard is no longer appropriate for meeting a requirement.

REGULATORY DEFINITIONS

According to the 1976 Medical Device Amendment to the Federal Food, Drug & Cosmetic Act, a medical device is defined as: “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, that is recognized in the official National Formulary, or the United States Pharmacopoeia, 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 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 principals intended purposes”. The FDA was given specific authority to regulate all “medical devices” in an effort to promote safety and efficacy.
Safety: There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.5

Efficacy: There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.6

MEDICAL DEVICE EVALUATION

The FDA is a federal body, directed by the Commissioner, which consists of a number of offices, divisions, and branches (Figure 1). Endoscopes and accessories which are introduced through the mouth, urethra, or anus are reviewed within the Division of Reproductive, Abdominal, and Radiological Devices (DRARD) by the Urology and Lithotripsy Devices Branch. Gastroenterology devices or accessories such as stents and catheters are reviewed by the Gastroenterology and Renal Devices Branch of DRARD. Disinfectants, sterilants, endoscope washers, and other types of reprocessors are reviewed by the Infection Control Devices Branch within the Division of Dental, Infection Control and General Hospital Devices (DDIGD).

CLASSIFICATION OF MEDICAL DEVICES

The FDA has established a three Class system based on the risk, technology, and characteristics of the device.2,7-9 All devices are classified into one of three categories:

Class I devices are considered to be low risk, and subject to the least regulatory control. They present minimal potential for harm to the user and are often simpler in design than Class II or Class III devices.

Class II devices are considered to moderate risk, and are those for which general controls alone are insufficient to assure safety and effectiveness, and existing methods are available to provide such assurances. Class II devices are also subject to special controls, which may include special labeling requirements, guidance documents, mandatory performance standards and postmarket surveillance.

Class III devices are considered to be high risk, for which insufficient information exists to assure safety and effectiveness solely through general or special controls. Premarket Approval (PMA) is the process by FDA to evaluate the safety and effectiveness of Class III devices, which may include bench tests, animal studies, and clinical trials conducted under an Investigational Device Exemption (IDE).

General Controls: These are baseline requirements for all devices under the Food, Drug and Cosmetic Act (FD&C Act). These include:

Registering and listing: Section 510 of the FD&C Act requires all US device manufacturers to register their establishments with FDA on form FDA-2891. They are also required to list their devices with FDA on form FDA-2892. These conditions must be met prior to commercial distribution by any manufacturing company. (21 CFR Part 807.20)

Comply with labeling regulation: All medical devices in US commerce must be properly labeled, as described in title 21 CFR Part 801, 809, or 812. They should never include any statements such as “FDA approval” to avoid the impression of official endorsement of the device.

Submit a pre-market notification: A pre-market notification [510 (k)] is a marketing application submitted to FDA to demonstrate that the medical device is as safe and as effective as a legally marketed device that was or is currently on the US market, and does not require any other pre-market approval (21 CFR part 807, subpart E). Most Class I devices are exempt from the [510(k)] requirement regulation. Class II and III devices are not (see below). In these cases, the manufacturer would have to submit a pre-market notification [510(k)] for Class II devices or a pre-market approval application for Class III devices to the FDA. The manufacturer cannot market the device until the firm receives a marketing clearance letter from the FDA.

Manufacture devices in accordance with the Good Manufacturing Practices (GMP) regulation: This regulation contains general quality assurance or quality system requirements in areas of importance to manufacturers of all finished devices. They include: building and environmental controls for personnel safety; device labeling, packaging, and evaluation for consumer safety; record keeping, complaint processing, and quality assurance system audits.

prohibition of adulterated or misbranded devices.

Special Controls: In addition to general controls, Class II devices (as defined in section 513 (a)(1)(B) of
the FD&C Act) include any device for which reasonable assurance of safety and effectiveness can be obtained by applying "special controls." These may include special labeling requirements, mandatory performance standards, voluntary standards, user information check-lists, patient registries, guidance documents, patient information/education and post-market surveillance.

**PreMarket Notification (510(k))**9-11: The majority of Class II devices are reviewed through the 510(k) process. This is an application submitted to the FDA demonstrating that the medical device under consideration meets one of the following criteria:

- It has the same intended use as a predicate device, and has the same technological characteristics OR
- It has the same intended use, does not have the same technological characteristics, but has been demonstrated to have the same safety and efficacy standards as the legally marketed predicate device.

A **predicate device** is a device that was legally marketed in the US prior to May 28, 1976, or one which has been marketed following that time, but has Class I or Class II status. If the FDA finds the device not to be substantially equivalent, the manufacturer may then re-submit the notification, petition the FDA for reclassification of the device, or submit a pre-market approval (PMA).

**Pre-market approval:** Class III devices are usually those that 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. Such devices require pre-market approval (PMA), which is the most stringent regulatory category for medical devices. These requirements are defined in 21 CFR part 814. They include a full pre-market submission with extensive review by the FDA staff. This review may include an independent FDA advisory panel in a public session, and is based upon the demonstration of "valid scientific evidence" that demonstrates safety and efficacy. Such a panel would consist of seven voting members, a non-voting industry representative, and a non-voting consumer representative. Usually consultants with special expertise are invited to be part of the panel.

Currently, a new pathway to market Class III devices has been developed, called the "Product Development Pathway (PDP)". This alternative to the PMA process was developed as part of recent efforts to streamline the FDA process.12 The focus of this pathway is to get the FDA and the medical device company to agree on what data is needed for device approval at the start of the regulatory process. In addition to bench and animal data, a proposed clinical trial protocol is presented to the panel, and specific success criteria for each end-point are determined in advance. If the protocol is approved, and the clinical trial yields data that meet or exceed these criteria, the process would be completed, and the device approved.

**NOTIFICATION**

After the technical review is completed, the reviewer’s recommendations are forwarded to the division director for concurrence and to the Office of Compliance (OC) to verify that the submitter is in good standing. This control mechanism is aimed at avoiding marketing clearance to manufacturers who may have significant violations of the Good Manufacturing Practices (GMP), or violations related to the unsafe and/or inefficacious following their release into the market. It requires that manufacturers track their devices into the market for malfunction and to report such problems to the FDA. Device users can also report problems directly to the FDA through the Medwatch program.

**RECOMMENDATIONS**

ASGE should promote and support this process by:

1. Participating in the design and conduct of studies evaluating the safety and effectiveness of new medical devices (pre-market evaluation);
2. Reporting to the manufacturers and to the FDA malfunctions and safety concerns related to new medical devices (post-market evaluation);
3. Active involvement in the development of national and international standards pertaining to gastrointestinal endoscopy; and
4. Participation on FDA Medical Device Advisory Panels. ASGE is the major society dedicated to the practice of gastrointestinal endoscopy, and can help by providing guidelines for device evaluation and impartial expert advice to FDA and industry throughout the review process.

**REFERENCES**

5. Title 21 Code of Federal Regulations (CFR) 860.7(d)(1).
7. FDA Classification of Medical Devices. (http://www.fda.gov/cdrh/dsma/dsmclas.html).

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