Communication from the ASGE Technology Committee

TECHNOLOGY STATUS EVALUATION REPORT

The role of the U.S. Food and Drug Administration in device evaluation and monitoring

The American Society for Gastrointestinal Endoscopy (ASGE) Technology Committee provides reviews of existing, new, or emerging endoscopic technologies that have an impact on the practice of GI endoscopy. Evidence-based methodology is used by performing a MEDLINE literature search to identify pertinent clinical studies on the topic and a MAUDE (U.S. Food and Drug Administration Center for Devices and Radiological Health) database search to identify the reported complications of a given technology. Both are supplemented by accessing the "related articles" feature of PubMed and by scrutinizing pertinent references cited by the identified studies.

Technology Status Evaluation Reports are drafted by 1 or 2 members of the ASGE Technology Committee, reviewed and edited by the committee as a whole, and approved by the Governing Board of the ASGE. When financial guidance is indicated, the most recent coding data and list prices at the time of publication are provided. For this review, the MEDLINE database was searched through October 2009 for articles and references related to devices and the U.S. Food and Drug Administration by using the keywords "FDA" and "devices." In addition, the Web was searched using the same keywords. The U.S. Food and Drug Administration website was also thoroughly reviewed. Practitioners should continue to monitor the medical literature for subsequent data about these issues.

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AGENCY OVERVIEW

The origin of medical device regulation in the United States dates back to 1906, after passage of the Food and Drug Act. This act and subsequent amendments gave the government power to interrupt sales of food and drugs that were unsafe or had misleading claims of effectiveness.[1] The U.S. Food and Drug Administration (FDA) was formed in 1927 to allow a more organized administration of the concepts of the Food and Drug Act. In 1938, the Federal Food, Drug, and Cosmetic Act was passed, which gave the FDA authority to seize adulterated or misbranded devices.

Shortcomings of the drug and device regulatory structure were becoming evident as more drugs and devices came on the market. There was an increasing need for premarket review of devices rather than just enforcement by seizure of problematic devices. The first step to address these problems came with the passage of the Drug Amendments of 1962 legislation. It was also becoming clear that devices should be treated differently from drugs and that no single form of regulation would be appropriate for all medical devices. The Medical Device Amendments of 1976[2] was an important landmark in device regulation, and most of the current structure of medical device regulation is based on this legislation. The field of regulation of medical devices is truly a work in progress and improvements were added with the Safe Medical Device Act (1990), the FDA Modernization Act (1997), the Medical Device User Fee and Modernization Act (2002), and the Food and Drug Administration Amendments Act (2007). The Safe Medical Device Act of 1990 was the first to be issued after the landmark 1976 Medical Device Amendments legislation and substantially increased the FDA's postmarket authority over medical devices as well as addressing other shortcomings of the Medical Device Amendments. The FDA Modernization Act of 1997 directed the FDA to use the "least burdensome" means of subjecting devices for approval. Addition of a user fee in 2002 was modeled on a similar drug user fee that was in use regarding approvals of pharmaceuticals. The Food and Drug Administration Amendments Act of 2007 had important provisions regarding improvement of regulations for devices used in pediatrics, an area that was not well-addressed previously. Each of these amendments was enacted to fill gaps in regulation that became apparent over time. These include specifying details of product recalls, product tracking, inclusion of humanitarian exemptions, postmarket surveillance enforcement authority, and other important FDA functions.

The Center for Devices and Radiological Health (CDRH) is the component of the FDA responsible for administering the regulatory function pertaining to medical devices (Fig. 1). The premarket review of devices used in gastroenterology is overseen by a branch of the CDRH,

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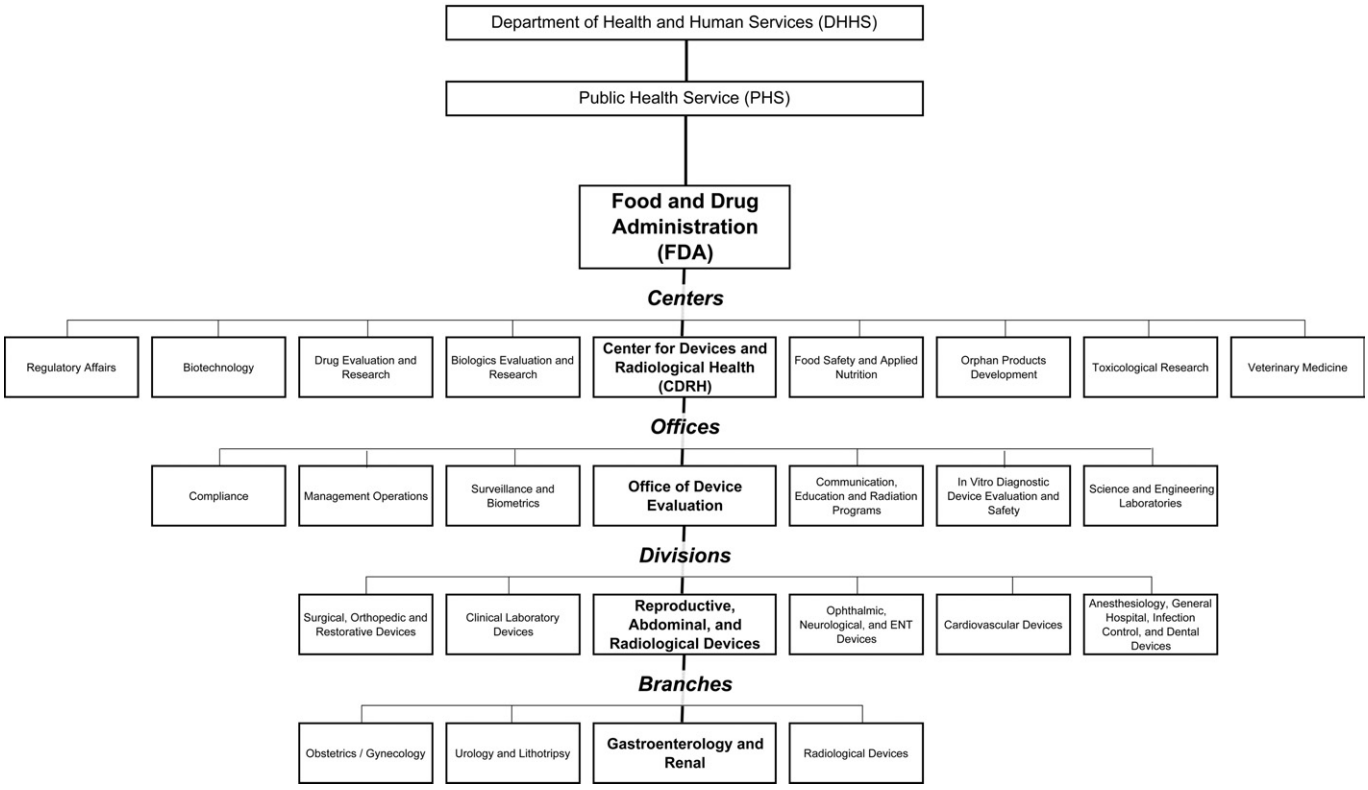

Figure 1. Organization of the U.S. Food and Drug Administration (FDA) as it pertains to devices used in gastroenterology.

the Office of Device Evaluations. Most GI devices are reviewed by the Division of Reproductive, Abdominal, and Radiological Devices, although endoscopy-related devices may come under the review of a different division (eg, automatic endoscope reprocessors reviewed by the Division of Dental, Infection Control, and General Hospital Devices).

The FDA through the CDRH is charged with enforcement of regulations pertaining to medical devices. These activities are broad and include review of manufacturing processes, distribution, labeling, product evaluation, clinical investigation, premarket review, postmarket performance review, and enforcement actions to ensure compliance with regulatory standards and processes.

DEVICE CLASSIFICATIONS AND REGULATORY REQUIREMENTS

Manufacturers of medical devices in the United States must comply with 7 basic requirements:[3] (1) registering their establishment with the FDA; (2) listing their device with the FDA according to generic categories outlined in federal regulations; (3) obtaining premarket clearance of the device before commercially marketing unless the category of device is exempt; (4) adhering to the Quality Systems regulations, also referred to as Good Manufacturing Practices (GMPs); (5) following device labeling requirements; (6) following the Medical Device Report (MDR) regulation and submitting death, serious injury, and malfunction reports to the FDA; (7) obtaining Investigational Device Exemption (IDE) when using unapproved devices for clinical studies.

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, which is 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 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 its primary intended purposes."[4] Some devices, such as drug-eluting coronary stents, act through a hybrid mechanism, but for the purpose of FDA regulation, are governed by the primary mode of action.

Medical devices, based on established generic descriptions, are classified by the FDA into 3 classes depending on the complexity of the device and perceived risk to the patient.[5] Class I devices are low risk, such as examination gloves and tongue blades. These are generally exempt from premarket review. Some Class I devices are also exempt from Quality Systems regulations. Safety and effectiveness of Class I devices are ensured by general controls (see later). Class II includes moderate-risk devices,

such as traditional endoscopes and many endoscopic accessories. In addition to general controls, some Class II devices also may be subject to special controls that vary by device type and most require premarket review through a premarket notification, a 510(k) application, before marketing (see later). Class III devices are those that are "life-supporting, life-sustaining, are of substantial importance in preventing impairment of human health or present a potential unreasonable risk of illness or injury." Examples include heart valves, ablation catheters, pacemakers, and breast implants. Class III devices require special premarket approval (PMA) based on finding "a reasonable assurance" of "safety and effectiveness" before marketing. These devices also receive closer postmarketing surveillance. Approximately 4000 Class I devices are introduced annually and do not need FDA evaluation before marketing. In 2007, 3052 devices had abbreviated reviews (Class II), and 41 devices (Class III) went through the PMA process.[6]

General controls apply to all 3 classes of medical devices. They include requirements for actions both before and after a device reaches the market. General controls require device manufacturers to register each manufacturing location with the FDA, list their marketed devices with the FDA, comply with device-labeling regulations, submit premarket notifications (unless exempt), follow quality system regulations (which incorporate GMP requirements) in device production, adhere to regulations banning adulterated and mislabeled devices, comply with regulations related to record keeping and reporting, and follow FDA requirements related to any notifications, recalls, or other actions associated with a defective device.

Special controls are intended to ensure the safety and effectiveness of Class II devices when general controls are not adequate to do so. Specific controls vary by device type. They may include special labeling requirements, guidance documents, performance standards, and required postmarket studies. Another type of special control, postmarket surveillance, may be ordered by the FDA for certain Class II or III devices. These orders can include the collection of clinical data. In rare cases, a device registry is required.

INTRODUCTION OF NEW DEVICES

All new medical devices need to be reviewed by the appropriate division of the CDRH. Most of the lowest risk Class I devices are exempt from the normal premarket review process. Class II devices that may have "substantial equivalence" to a previously legally marketed device can go through a 510(k) application. A device already in use is called a predicate device. The manufacturer must notify the FDA of its intent to market such a device; this is termed premarket notification. The 510(k) application process requires the manufacturer to provide evidence that the device to be introduced is substantially equivalent to a predicate device (ie, has the same intended use and is at least as safe and as effective as the predicate device, and does not raise any new types of safety or effectiveness questions). Data to support the similarities to the predicate device should be included in the 510(k) application. Data are normally in the form of bench and animal studies; however, in a small number of Class II devices, clinical data may be needed to establish substantial equivalence. The ability of a manufacturer to get 510(k) clearance for a device is normally faster and less expensive compared with the PMA process in which extensive clinical studies demonstrating safety and effectiveness are usually needed. It also requires less use of resources by the FDA.[7] The regulations pertaining to the 510(k) process were designed to limit burden and obstruction to the introduction of new devices. The process is a balance between protecting public health while at the same time not adding regulatory obstruction to the timely availability of new products.

A device substantially different from existing devices must undergo a PMA application process, the most stringent new device application. This applies to all Class III devices. Class III devices are those for which insufficient information exists to ensure safety and effectiveness solely through general and special controls. Therefore, the PMA requires detailed information about product safety and effectiveness. Nonclinical and clinical testing may be required by the FDA. In addition, based on the perceived risk of the device, the FDA may order the manufacturer to undertake a postmarket study as a condition of granting approval. Since 2002, manufacturers are required to pay filing fees for the review of 510(k) submissions and PMA applications. One major objective of this legislation was to help speed the clearance or approval of devices by augmenting FDA resources. Device user fees are only allowed to be used for evaluating condition-of-approval postmarket studies and identifying premarket safety and effectiveness issues for devices.

An Investigational Device Exemption (IDE) can be requested and issued to a manufacturer or a sponsor in order for human studies to be conducted to assess the safety and effectiveness of a device for a given indication. These clinical performance data are used for research or to support a 510(k) or PMA application. The IDE can be used at a specific institution after approval by the local institutional review board.[8] Studies of devices with significant risk must be approved by the FDA and local institutional review board before the study can begin. Although most IDEs are issued to permit use of devices before a PMA application, they may also be used for the small percentage of 510(k) submissions that require clinical data to support the claim of substantial equivalence to a predicate device. The FDA also has the authority to order surveillance studies for certain categories of devices after they have been cleared or approved; these studies are known as Section 522 studies.

POSTMARKET EVALUATION

Once finished devices have been cleared or approved for marketing, manufacturers of the finished devices must adhere to Quality Systems Regulations, which include the operational procedures (GMPs). These regulations require specific building and environmental controls for personnel safety as well as methods, record keeping, and controls used for manufacturing, packaging, labeling, storing, and servicing devices. The FDA is authorized to perform inspections to confirm compliance, and failure to comply with GMPs is a common source of regulatory action, including product recall. In the case of serious negligence in GMPs, the agency has the capacity to refer the matter to the Department of Justice.

After FDA clearance or approval and subsequent marketing of a medical device by a manufacturer, adverse events may occur. Often, these are events that may not have been uncovered in the course of the clinical trials. Therefore, it is very important to have adequate postmarket evaluation of devices. In response to problems with timely reporting of adverse effects related to defective heart valves in the 1980s, legislation was enacted in 1990 and 1992 to strengthen postmarket surveillance. Postmarket surveillance is carried out by the Office of Surveillance and Biometrics of the CDRH. Some of these measures include specific tracking of certain high-risk devices, requirements for manufacturer reporting of serious device-related injuries or deaths, spontaneous reporting systems, field inspection of facilities, and analysis of databases, registries, and scientific studies. The FDA may issue a safety alert regarding a problem with a device that poses a risk of substantial harm. In these cases, the CDRH issues a Public Health Notification to make the health care community aware of the risk associated with the use of a medical device and provides recommendations to avoid or reduce the risk.

Most of the postmarket surveillance that occurs involves what are termed spontaneous reporting systems. Manufacturers are required to report medical device events whenever they discover that their device may have caused or contributed to a serious injury or death or may have malfunctioned and the malfunction would be likely to cause or contribute to a death or serious injury if it were to recur. Hospitals and other user facilities are required to report device-related deaths to the manufacturer and FDA, and device-related serious injuries to the manufacturer or the FDA if the manufacturer is unknown. In distinction to manufacturers, hospitals and other user facilities, end users (physicians and other medical personnel) do not have a legal obligation to report medical device events, but are encouraged to report events to their facility's designated MDR contact or to do so voluntarily through FDA's MedWatch program.

In 1992, the MedWatch program was introduced as a way to make it easier for users, including health care professionals and patients, to report device-related adverse effects to the FDA. Events can be reported by telephone, fax, or logging onto the MedWatch site at www.fda.gov/medwatch.

Currently, all reported problems are investigated, and since 1995, the results of the investigation have been collected on the Manufacturer and User Device Experience (MAUDE) database. This searchable database is available for public access and contains Freedom of Information releasable data related to reported events.[9] Individual reports within the system do not result in restrictions or safety alerts, but potentially allows patterns of problems to be identified that could trigger further inquiry and potential enforcement actions.

Health care workers who have a problem with a medical device do not have a legal obligation to report the problem to either the manufacturer or to MedWatch. Not surprisingly, this leads to underreporting of adverse events. Health care facilities are required to report device-related deaths or serious injury, and designating an individual as an MDR contact can help facilitate this reporting by health care workers. In addition, manufacturers are required only to report events of which they become aware, but are not required to actively seek out problems with devices. This can lead to a reactive rather than proactive surveillance arrangement, with investigation after injuries may have already occurred. The FDA has the authority to require additional postmarket surveillance on devices that are thought to be a potential source of risk.

The FDA Modernization Act of 1997 directed the FDA to develop a new system for adverse event reporting by a subset of user facilities that offers a representative profile of user reports of deaths and serious illnesses or injuries related to a device. This system is known as the Medical Product Surveillance Network or MedSun.[10] Currently, there are approximately 350 facilities participating in the MedSun network selected on a number of factors including the size and location of the facility. The objective is to have a representative sample of device user facilities, and participants include large teaching facilities, small hospitals, urban hospitals, suburban hospitals, nursing homes, outpatient diagnostic and treatment facilities, and home health services. MedSun participants agree to submit both mandatory and voluntary user facility reports. If participants submit an adverse event report that is mandated under current regulations, MedSun staff forward the report to the manufacturer. For voluntary reports (eg, "close calls" that do not result in harm), participants can tell MedSun staff whether they want such reports to be forwarded (although the FDA encourages such forwarding). The MedSun program is a work in progress, and information gathered from this network of reporting facilities is expected to be a model to increase the reliability and accuracy of adverse device events.

MEDICAL DEVICE RECALLS AND CORRECTIONS

If the FDA or a manufacturer determines that there is a problem with a device, the manufacturer may voluntarily withdraw or correct the device or the FDA may order a recall. Although the FDA has the authority and is mandated to order a recall for devices posing serious health hazards, manufacturers often voluntarily recall hazardous devices before the FDA takes this action. A product recall is the most extreme measure that can be applied to a defective or hazardous device, and usually other steps are sufficient. The manufacturer may make a correction that may entail instituting a repair or modification to a device without completely withdrawing it from use. A Class I recall involves a situation in which there is a reasonable probability that the use of or exposure to the product will cause serious adverse health consequences or death.[11] Class II and III recalls involve situations in which patient injury is less likely or not likely, respectively. Approximately 500 to 600 devices are recalled each year, typically initiated by the manufacturer.[12] Of these, there are approximately 10 to 25 Class I recalls each year.[13] Recalls and public health notifications are posted on the FDA's weekly enforcement report.[14] The FDA publicizes a recall only when it believes that the public needs to be alerted to a serious hazard.

MEDICAL DEVICE TRACKING

The tracking of medical devices is intended to assist the prompt notification of users when a device presents a serious, immediate risk to health and to speed the recall of such a device when appropriate. The FDA currently requires tracking for 12 implantable devices and 4 devices used outside hospitals. Examples of such devices include temporomandibular joint prostheses, implantable pacemaker pulse generators, mechanical heart valves, ventricular bypass assist devices, and implantable infusion pumps. Manufacturers should be able to provide key information to the FDA about the location of a tracked device within 10 working days for devices that have already been distributed to patients and within 3 days for those that have not.

OFF-LABEL USE OF DEVICES

Use of medical devices in a manner that is different from the initial FDA clearance or approval, as listed on the manufacturer's label or summary description of the device, is termed off-label use. The FDA does not have the authority to regulate medical practice. Hence, once a device is cleared or approved for marketing, physicians may use the device for indications that are not mentioned or specifically restricted in the device's labeling. This is considered part of the practice of medicine, which the FDA does not regulate. Manufacturers are not allowed to recommend or market off-label use of their device. Off-label use of devices can extend the range of use of a device, for example, when a device indicated for use in adults is used in pediatric populations. Rarely, problems with off-label use of a device can result in an FDA action in the form of a product recall. Such an example occurred in 2004 when some biliary stents were used in the vascular tree.[15] Several cases of serious patient injury occurred, resulting in the FDA recalling not the device, but the instructions for use packaged with the device.

HUMANITARIAN DEVICE EXEMPTIONS

In addition to the clearance and approval processes described, Congress has allowed devices to be approved for marketing under a Humanitarian Device Exemption. To qualify, a device must be intended for patients with a rare disease or condition (fewer than 4000 persons in the United States per year) for which no comparable previously approved device is available. Among other requirements, manufacturers seeking a Humanitarian Device Exemption must present evidence that there is a reasonable assurance of product safety when the device is used as proposed and that the probable health benefits of the device outweigh the potential for harm, taking into account the risks and probable benefits of available alternative therapies. Evidence of effectiveness is not required. Granting of a Humanitarian Device Exemption allows a company to market a device as a Humanitarian Use Device. Such a device can only be used in a health care facility after institutional review board approval and continuing review.

The FDA may allow clinical use of unapproved devices in other situations, including certain emergency situations and certain situations in which a clinical study has been completed, but the marketing application has not yet been approved. Under so-called compassionate use provisions, the FDA may allow use of an investigational device when it might benefit a patient who does not meet criteria for inclusion in research but who has a serious medical condition and no satisfactory alternative.

CONCLUSIONS

Although growth of new technology has prospered, funding of the FDA's mission has struggled to keep pace. In 2005, The Institute of Medicine concluded that the FDA "lacks the resources needed to accomplish its large and complex mission today, let alone to position itself for an increasingly challenging future."[2] In attempt to match the pace of technologic progress, the process of device regulation has evolved over the years. With more experience with new devices, needed areas of improvement have become apparent. One such area is the evaluation of

devices in the pediatric population. Recent legislation with the FDA Amendments Act of 2007 has strengthened this area.

The current process by which medical devices are cleared by the FDA was developed so that the process would be flexible enough to handle the wide range of devices while not being unduly time-consuming and burdensome. The framework established by the Medical Device Amendments of 1976 remains in place to this day and has undergone incremental improvements as shortcomings are identified. The 510(k) application process has allowed timely introduction of medical devices. Device monitoring after introduction continues to be of paramount importance, and a system for regulation of this continues to be improved. The intensity of monitoring is tailored to the specific needs of the device. The CDRH is developing risk-assessment criteria that consider the probability and severity of harm and allocate resources for monitoring those devices and manufacturers that present the greatest risk to public health.

The CDRH has also taken steps to strengthen adverse event reporting and to improve communication with users of medical devices and in general has tried to place more emphasis on postmarket follow-up to more proactively detect adverse events. The MedSun program was instituted as a targeted surveillance system of adverse event monitoring, and funds have been committed to expansion of this effort. Every medical professional should make an effort to report problems with medical devices through the FDA MedWatch program because this is often the only mechanism by which systematic problems can be discovered. Medical devices used in GI endoscopy will continue to evolve in complexity, and the system of premarket evaluation and postmarket monitoring will likewise need to adjust to maximize patient safety and clinical outcomes.

Abbreviations: CDRH, Center for Devices and Radiological Health; FDA, U.S. Food and Drug Administration; GMPs, Good Manufacturing Practices; IDE, Investigational Device Exemption; MDR, Medical Device Report; PMA, premarket approval.

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