

Cosmetic Medical Devices and Their FDA Regulation

CLINICAL DERMATOLOGY PRACTICE HAS EXPANDED to include the use of many procedures and devices for cosmetic purposes. This is a consequence of not only the rising interest in aesthetic medicine but also the economic pressures on the practitioner participating in managed care plans, as well as increasing regulation and requirements of office practice. However, the increased reliance on new cosmetic procedures and devices has resulted in confusion over their real benefits and risks. This confusion has arisen, in part, as a result of aggressive marketing by manufacturers. For example, entering the cacophonous technical exhibits hall at the American Academy of Dermatology meeting is an experience similar to walking in the Central Bazaar in Istanbul, where myriad merchants are plying their wares, each exhorting the superiority of his product over that of his neighbor.

Many practitioners greet these innovative devices with unbridled enthusiasm, which tempers over time as the disadvantages and risks become apparent. It is clear that many physicians who use these products to enhance their patients' appearance do not understand the US Food and Drug Administration (FDA) approval process for devices such as lasers and injectable dermal fillers. Without this knowledge, the physician is limited in understanding the safety and effectiveness of the devices and may not be advising or treating the patient appropriately.

To determine what is best for our patients, we must become better informed about the benefits and risks of these devices, rather than relying solely on the sales force of the company entreating us to purchase their "FDA approved" device. Many physicians erroneously seem to believe that FDA approval of a device is paramount to receiving the Good Housekeeping Seal of Approval. Rather, it is more appropriately likened to an Underwriters Laboratories (UL) listing. For example, the electrical socket with the UL label is approved for a particular use, but improper use will give you a nasty shock. Similarly, FDA approval is granted for a specific use with specific indications, and this information is available in the manufacturer's labeling and instructions for use of the device. The approval does *not* imply that the device is safe for every use or indication.

Physicians are familiar with the FDA requirements for drug approval but much less knowledgeable about the different regulations that apply to medical device approvals for the marketplace. After a drug or device is approved, the adverse cutaneous reactions such as those described in this issue of the ARCHIVES¹⁻⁴ become known. Careful reporting of such events is far less stringent in the postapproval marketing phase than in the preapproval period. It behooves the physician to understand

the data supporting the risks and benefits of a medical device, as well as the limitations of the evaluation of these devices because only then can he or she use the device in a safe and effective manner.

MEDICAL DEVICE AMENDMENTS OF 1976

The term *medical devices* refers to a vast array of implementations used in the practice of medicine to enhance the health of the patient. A *device* is defined, in pertinent part, 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 . . . [or that may] affect the structure or any function of the body."⁵ Unlike drugs and biological agents, devices do not achieve their primary intended use through chemical action, nor are they dependent on being metabolized for the achievement of their primary intended purposes.⁶

Most people, including physicians, are not very knowledgeable about the sources of the FDA's authority or the limits of its power. Modern regulation of medical devices falls under the jurisdiction of the Center for Devices and Radiological Health (CDRH).^{7,8} Prior to that time, device regulation was very limited under the Food Drug and Cosmetic Act of 1938,^{7,8} and was primarily geared toward the prevention of economic fraud. However, experience with the Dalkon Shield (A.H. Robins Co, Richmond, Va) made the establishment of a more rigorous regulatory environment for public safety de rigueur.

When the risks of this device became obvious, Congress recognized the danger of unregulated devices as well as the dangers of inaccurate claims by manufacturers and enacted the 1976 Amendments.^{7,8} While devices on the market prior to the 1976 Amendments did not require FDA review of their safety and effectiveness, the 1976 Amendments mandated clear pathways for bringing new devices to market, established device classes based on risk, and created external advisory panels to review the results of the premarket studies.

Device Classification

With these Amendments,^{7,8} Congress specifically recognized the great diversity in the function, complexity, and risk involved in the use of devices. This variability led to the classification of devices, each with separate guidelines for regulation, which allow for calibration of the regulatory controls for different types of devices.⁹

Class I. For the lowest-level devices, general controls (ie, adherence to good manufacturing practices, labeling regu-

lations, quality systems regulation, and record keeping) are sufficient to provide assurance of safety and effectiveness. Examples of class I devices include tongue depressors, gauze, scalpels, stethoscopes, and nonpowered breast pumps. Today, most class I devices do not require FDA review prior to marketing.

Class II. These devices require some special controls such as guidance documents, performance standards, patient registries, and/or postmarket surveillance in addition to the general controls. Examples include sutures, lasers, intense pulsed-light devices, ultrasound devices for deep heating, liposuction systems, radiofrequency units, hyfrecators, and UV boxes for therapeutic indications. With very few exceptions, class II devices are reviewed in premarket notifications, called 510(k) submissions, to the FDA.¹⁰

Class III. These devices are defined as those for which insufficient information exists to assure safety and effectiveness solely through general or special controls. Class III devices also include those that are represented "to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health."¹¹ Such a device requires more extensive study because it may present a potential unreasonable risk of illness or injury if used improperly. Examples of class III devices include neurologic stents, heart valves, implanted neuromuscular stimulators, medical image analyzers, and cochlear and breast implants. Examples in the dermatologists' therapeutic armamentarium include cellular wound dressings and injectable dermal fillers.

Premarket Approval

The pathways to bring most complex medical devices (class II or III) to market are either a "Pre-Market Approval" (PMA) application or a 510(k) submission.¹⁰ A breakthrough device is generally approved with a PMA. This may be for a new indication for a previously marketed device or a new technology that raises new types of questions of safety or effectiveness. The manufacturer must submit safety and effectiveness information for the specific use and demonstrate a favorable benefit/risk ratio.

The PMA includes reports of all prior testing of the devices, including laboratory studies of microbiology, toxicology, immunology, biocompatibility, chemistry, mechanical-strength testing, stress-wear testing, sterilization, and shelf-life data. The PMA also includes information on the manufacturing processes and facilities and all clinical data collected both within and outside of the United States, statistical analyses of the data, and labeling. The FDA inspects the manufacturing facility and audits some of the clinical sites to assess whether the study was conducted in accordance with the protocol and whether the data are reliable. Manufacturers of injectable dermal fillers approved in the United States such as Zyderm (Inamed Corp, Santa Barbara, Calif), Zylplast (Inamed Corp), Restylane (Medicis Aesthetics Inc, Scottsdale, Ariz), Sculptra (Dermik Laboratories, Ber-

wyn, Pa), and Hylaform (Inamed Corp) have provided this type of information prior to their approval.

Most devices in the United States (approximately 98%) are class II devices and are approved via the 510(k) application, in which the safety and effectiveness of a device are compared with those of a "substantially equivalent" commercially available device. The FDA action on a 510(k) application is faster than on a PMA (90 days vs 180 days), less costly to the manufacturer (average cost, \$3000 vs \$300 000), and requires less premarket testing. The 510(k) process does not require clinical data; in fact, only 10% of 510(k) applications have any clinical data at all. It is the "least burdensome" method for getting a device to market defined in the FDA Modernization Act of 1997.¹² This Act also provides for early collaboration with the FDA in device protocols for development to make the development and approval process more efficient and less expensive. Most lasers, radiofrequency devices, intense pulsed-light systems, and surgical facial implants have been approved by this pathway.

There are some obvious paradoxes in the regulatory framework for devices, particularly with the 510(k) pathway. A device may be approved by this method when the manufacturer shows that its function, safety, and effectiveness are substantially equivalent to those of a device already on the market and that may have been on the market since prior to 1976 (and thus approved under the older, less stringent regulatory framework). Subsequently, the device may be touted as an innovative, advanced product. So we must ask, which is more accurate, the claim of similarity to a pre-1976 device proposed to the FDA, or the claim of uniqueness advertised to the consumer? In any case, the physician should be aware that the specific device may have never been tested with clinical trials to assess its safety and effectiveness but may have relied on laboratory or animal studies.

MEDICAL DEVICE APPROVAL VS DRUG APPROVAL

The drug corollary for a PMA is a new drug application (NDA). New drug applications include precise and detailed animal data and data on toxicology, pharmacology, pharmacokinetics, and interactions with other drugs. Drug approval end points are determined according to the drug class, eg, microbiologic cure, cancer remission, or other class. Drug development generally takes 7 to 9 years from the time the molecule is synthesized until it is in the pharmacy, and the cost of drug research and development, on average, exceeds \$800 000 000,¹³ which is vastly greater than that of a device.

There is no analogue for the 510(k) process for drugs. The FDA receives a similar number of PMA applications and NDAs each year. However, the FDA reviews more than 4000 510(k) applications annually.¹⁴ The patent protection for a drug molecule lasts 20 years from the date of filing; the market lifetime for most devices is shorter because most devices undergo frequent modifications and improvements in their design and features.

The FDA regulates device design, manufacturing processes, labeling, and promotional advertising, but it does

not interfere with the free exchange of ideas. Currently, there is a gray zone in promotion of these devices, particularly in the areas of lasers and other irradiation or wave-emitting devices. It is not in the purview of the FDA to regulate the practice of medicine. The US Congress was very clear when writing the law governing the FDA that it does not regulate which physicians can use these devices, nor how they use them in the practice of medicine. The FDA regulates only the industry that sells and distributes these devices.

GUIDELINES FOR PRESCRIBING AND USING MEDICAL DEVICES

It is increasingly evident that to provide the best guidance to patients, we must exercise due diligence. We have an obligation to use medical devices safely, and doing so requires that we (1) learn the risks as well as the benefits, (2) be knowledgeable about which patients are most likely and least likely to benefit or be harmed by a medical device, and (3) develop our techniques to reduce the risks. With these devices, which are tools, clinical outcomes are more dependent on the expertise and judgment of the practitioner. Unfortunately, few physicians take the time to read the small print in the package insert or information accompanying the medical equipment. The following checklist should help physicians use medical devices most effectively:

- DO understand the extent and the limitations of the testing. If the product has been approved by a PMA, get a clear understanding of the success/failure statistics. Examine closely the safety issues and contraindications, and check the sex and ethnicity of the test populations.

- DO ask to see the safety and effectiveness data if the device has been cleared for marketing by a 510(k) application. (The PMA would have the clinical data in the labeling in the package insert.) Most clinical information you are provided for 510(k)-approved devices consists of a white paper developed for marketing purposes, which would not withstand scrutiny in a good peer-reviewed journal. If the manufacturer cannot provide real data, perhaps there is not sufficient evidence to use the technology at this time.

- DON'T jump on the bandwagon as a result of marketing pressure. Some adverse effects may take time to manifest. This is particularly important in new technologies. Consider, for example, Thermage (Thermage Inc, Hayward, Calif) radiofrequency device treatments that were touted on the Oprah Winfrey show.¹⁵ Myriad patients rushed to undergo the procedure described there. As of September 2005, there have been 155 adverse events reported on the Manufacturer and User Facility Device Experience (MAUDE) database.¹⁶ A substantial proportion of these events were the development of fat atrophy and scarring 3 or more months after the procedure. Subsequently, the manufacturer recognized the problem and changed the treatment algorithm. Hopefully, the new treatment parameters will avoid or mitigate these sequelae.

- DO search the CDRH database (<http://www.fda.gov/cdrh/databases.html>) if you are uncertain about a de-

vice's indications for use. For example, if you select the 510(k) Premarket Notification database and enter any descriptive information that you know about the device in question, the search will lead you to the letter from the FDA granting the permission to commercially distribute the device and containing the specific indications for use.

- DO exercise caution if you are using a device for an off-label indication. Make sure you have a sound rationale and adequate scientific information to justify its use.¹⁷ Maintain complete records for the product use and its effects. In the case of fillers, remember that a substance may behave very differently in one tissue or organ than in another. Here are some specific examples with potential risks:

Sculptra (poly-L-lactic acid), which is FDA approved for lipatrophy in patients with human immunodeficiency virus, has been used as a wrinkle filler, despite the lack of a clinical trial on the effects in the immunocompetent patient. If you use this substance in an immunocompetent patient, you are obligated to inform that individual that there are no safety data available and why you believe the treatment is of benefit to that person. Recently published case reports highlight some significant hazards encountered with its use in immunocompetent individuals, manifesting many months after administration.¹⁸

Radiesse (calcium hydroxyapatite; Bioform Medical Inc, San Mateo, Calif), which is FDA approved for use in bone augmentation, is not approved for the indication of cosmetic use as a wrinkle filler, although physicians are using it for that purpose. There are no long-term studies of the effect of this radiopaque substance in the skin.

Silikon (liquid injectable silicone; Richard-James, Peabody, Mass) and Adatosil (liquid injectable silicone; Chiron Vision Corp, Irvine, Calif) are approved for the installation in the eye globe (an immunologically privileged site) to treat retinal detachment, after which they are evacuated by aspiration from the globe generally in less than 6 months. There are no long-term prospective studies in immunocompetent individuals at this time for the use of either product as a wrinkle filler.

- DO report adverse reactions and medical device problems to the FDA. The MedWatch system (<http://www.fda.gov/medwatch>) is the FDA's safety information and adverse event reporting system. This is how you, the physician, can report a serious adverse event or problem that you suspect is associated with the use of a commercially available device. The MedWatch Web site contains information about how to submit a report online, by mail, or by telephone.

- DO become adept at using the FDA Web site to look at adverse event reports. These data are updated frequently to keep both the professional and the public informed about safety issues. The CDRH reports of adverse events involving medical devices can be searched online in the MAUDE database (<http://www.fda.gov/cdrh/maude.html>). While not a comprehensive record of all adverse events experienced (it is estimated that only 1%-2% of reportable events actually get reported), it does

provide information on the types of serious adverse events that have occurred.

CONCLUSIONS

Physicians must take more control of the marketplace to adequately protect our patients. We are confronted daily by patients requesting medications and procedures in response to direct-to-consumer marketing. There is powerful enticement in the positioning of these devices on television and in print media, with physicians providing testimonials about the benefit of their use. These physicians are often consultants paid by the device manufacturers. Consumer demand for these procedures is currently market driven. If we do not require documentation on real clinical effectiveness and safety, and if we purchase these devices based on trust rather than on sound science, then there is no incentive for the manufacturers to improve their track record. We can have a powerful impact on the safety of cosmetic procedures and devices for aesthetic uses if we understand how they have been studied and are labeled and if we demand scientific diligence. In this way, we will fulfill our obligation to our patients and to our profession.

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ARCHIVES Web Quiz Winner

Congratulations to the winner of our November quiz, Shaila N. Shah, MD, professor and head, Department of Pathology, Medical College, Bhavnagar, Gujarat, India. The correct answer to our November challenge was chordoma. For a complete discussion of this case, see the Off-Center Fold section in the December ARCHIVES (Dubroff RP, Maki RG, Busam KJ, Sachs DL. Bluish papule in a middle-aged man. *Arch Dermatol*. 2005; 141:1595-1600).

Be sure to visit the *Archives of Dermatology* Web site (<http://www.archdermatol.com>) to try your hand at the interactive quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month's print edition of the ARCHIVES. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also receive a free copy of *The Art of JAMA II*.