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The U.S. Approval Process for Medical Devices: Legislative Issues and Comparison with the Drug Model

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The U.S. Approval Process for Medical Devices: Legislative Issues and Comparison with the Drug Model

Summary

In response to highly publicized cases concerning the safety of prescription drugs and medical devices erupted, Congress convened several hearings in 2004 to examine the effectiveness of the U.S. Food and Drug Administration's (FDA) review processes for new medical products. In three cases, information was available to demonstrate that certain drugs might be unsafe and/or ineffective, yet they continued to be marketed and prescribed. Legislation introduced in the 109th Congress (the Fair Access to Clinical Trials Act, S. 470) seeks to improve drug safety by requiring more transparency in disclosing pre- and postmarket clinical trials of FDA's regulated medical products, including drugs, devices, and biologicals (among other trials). The legislation would also impose requirements for the disclosure of financial conflicts of interest between investigators and manufacturers. The broad scope of similar legislation proposed during the 108th Congress (S. 2933 and H.R. 5252) led some to question the appropriateness of applying disclosure requirements to the medical device industry, given differences in the way drugs and devices are approved and in the nature of the industry and product development. Legislation was not passed in the 108th, and debate on whether FDA's pre- and postmarket review processes are sufficient to protect the public from unsafe medical products is likely to continue in the 109th Congress, particularly with regard to the balance between timeliness and substance of premarket review, the adequacy of postmarket surveillance mechanisms, and the disclosure of clinical data.

The medical device market is diverse: surgical and medical supplies constitute the largest sector, followed by *in vitro* diagnostics (IVDs), cardiovascular devices, orthopedic devices and diagnostic imaging. Medical devices can be legally marketed in the United States in several ways. First, they are classified according to the risk that is posed to the patient from their use or misuse. The classification determines the type of premarket application, if any, that FDA will require. The higher the risk, the more stringent the premarket review conducted for approval. If a product is exempt from premarket review, the manufacturer need only register its facilities, list its devices with FDA, and follow general controls requirements. If premarket review is required, manufacturers can demonstrate substantial equivalence of their device with a legally marketed device, or can demonstrate that it is safe and effective on its own merits for the purpose intended by the company. Once approved, all manufacturers are required to report serious adverse events associated with the use of their devices to FDA. In addition, tracking is required for some medical devices. In many ways, the device-approval process is more flexible than that for drugs, with the majority of devices being cleared or approved without being evaluated in a true clinical trial.

This report, which will be updated, describes FDA's approval process for medical devices, compares it with the approval process for drugs, and serves as a primer for broader discussions of the impact of various legislative options aimed at maximizing both patient safety and availability of beneficial medical products. For more information about the U.S. drug approval process, see CRS Report RL32797: *Drug Safety and Effectiveness: Issues and Action Options After FDA Approval*.

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Overview of Legislative Issues

Introduction

In response to highly publicized cases concerning the safety of prescription drugs and medical devices erupted, Congress convened several hearings in 2004 to examine the effectiveness of the U.S. Food and Drug Administration's (FDA) review processes for new medical products.¹ At these hearings, some Members raised questions as to FDA's capacity or willingness to enforce safety requirements, including FDA-ordered follow-up studies for products approved by the agency. One overarching question for Congress is: Does FDA have the proper statutory tools and regulatory authority it needs to fulfill its public health mission? If not, what additional steps need to be taken? If it does, what are the barriers to enforcing the current laws? Debate on whether FDA's pre- and postmarket review processes are sufficient to protect the public from unsafe medical products is likely to continue in the 109th Congress, particularly with regard to the balance between timeliness and substance of premarket review, the adequacy of postmarket surveillance and the disclosure of clinical data. Two of the selected cases below illustrate the drug safety questions that triggered congressional interest in FDA's process for monitoring the safety of medical products. Two other cases demonstrate how the questions and issues surrounding FDA's assessments of safety and efficacy may also extend to medical devices.

Two hearings in 2004 investigated whether several drug manufacturers withheld evidence from the public that their antidepressant drugs were unsafe, or, at best, ineffective, in the treatment of pediatric patients.² Beginning in June 2003, British

¹ U.S. Congress, House of Representatives, Committee on Energy and Commerce, Subcommittee on Oversight and Investigation, *Publication and Disclosure Issues in Anti-Depressant Pediatric Clinical Trials*, Sept. 9, 2004 (Serial no. 108-121); and *FDA's Role in Protecting the Public Health: Examining FDA's Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children* Sept. 23, 2004 (Serial no. 108-125); U.S. Congress, Senate, Committee on Finance, *FDA, Merck and Vioxx: Putting Patient Safety First?* Nov. 18, 2004, [<http://finance.senate.gov/sitepages/hearing111804.htm>].

² Since 1987, nine drugs have been approved for treatment of depression in adults. Questions about the safety and effectiveness of antidepressant drugs have been raised publicly as early as 1991. Despite these questions and FDA's silence on pediatric use, U.S.

(continued...)

drug regulators issued strong recommendations against prescribing certain antidepressants for children.³ Following regulatory action in the United Kingdom, questions arose concerning the FDA's failure to take similar measures. On October 15, 2004, the FDA formally requested that manufacturers of the drugs include expanded and prominent warnings in their labeling, and issued a Public Health Advisory warning health care providers and patients of the added risk.

Another hearing received testimony concerning the anti-inflammatory drug, Vioxx, which was primarily used to treat arthritis. On September 30, 2004, Merck & Co., Inc. notified the FDA that it was withdrawing its product Vioxx⁴ from the market in response to recent study results that indicated an increased risk of heart attacks and sudden cardiac deaths in users. Some praised Merck's quick and decisive response; others (e.g., scientists, researchers, consumers, and physicians) claimed that data indicating the adverse cardiac effects had been available for at least the last three years. An estimated 93 million Vioxx prescriptions were reported to have been written since the drug's introduction in 1999.

Though not the subject of a congressional hearing in the 108th Congress, two similar market withdrawals occurred in the medical device industry. In July 2004, Boston Scientific Corporation withdrew two products from the market.⁵ The Express^{2TM} (Bare metal) Coronary Stent⁶ and the TaxusTM Express^{2TM} (paclitaxel-eluting) Coronary Stent were recalled because characteristics in the design resulted in the failure of the balloon to deflate and impeded removal of the balloon after the stent was placed in the coronary artery. Several years prior to the 2004 recall, device failures involving the balloon were reported with a different product, the NIR ON Ranger w/SOX cardiac stent. On September 17, 1998, Boston Scientific's chairman

² (...continued)

doctors wrote 10.8 million prescriptions for antidepressants for children and adolescents in 2002 (some children get more than one prescription per year). See "Helping Depressed Children," *Nature*, vol. 431, Sept. 9, 2004, p. 111.

³ Only Prozac was found to have a beneficial effect in children. See the Statement of the Medicines and Healthcare Products Regulatory Agency at [<http://www.mhra.gov.uk>], updated Feb. 2004.

⁴ Vioxx (rofecoxib) is a nonsteroidal anti-inflammatory drug (NSAID) that selectively inhibits cyclooxygenase-2 (COX-2). NSAIDs are used primarily for pain relief. COX-2 inhibitors are thought to provide additional benefit over older NSAIDs (such as ibuprofen and naproxen) by reducing the intensity and/or frequency of adverse gastrointestinal events. Other COX-2 inhibitors are Pfizer's Celebrex (celecoxib) and Bextra (valdecoxib).

⁵ See Medical Device Recalls, *Class I Recall: Boston Scientific Express Coronary Stent*, at [<http://www.fda.gov/cdrh/recalls/recall-071604.html>], and Medical Device Recalls, *Class I Recall: Boston Scientific Taxus Express Coronary Stent*, at [<http://www.fda.gov/cdrh/recalls/recall-070104.html>].

⁶ A cardiac stent is usually a slotted stainless steel tube or coil meshwork that is inserted into a blocked artery during an operation. Once the stent is inserted, the cardiologist uses saline to inflate a balloon in the stent, causing it to expand and hold the artery open. Over time, the artery may collapse or re-close (called restenosis). A drug-eluting stent is a normal metal stent that has been coated with a drug known to interfere with the process of restenosis.

and chief executive officer indicated the company's awareness of potential problems in a conference call to advisors and business partners.⁷ Despite the acknowledgment, the company continued to ship thousands of stents while negotiating with FDA to avoid a recall. On October 5, 1998, the company issued a recall of the defective product. Also in 1998, the company disclosed an ongoing criminal investigation by the Department of Justice surrounding the firm's decision to delay the recall. Though the company is still under investigation, a recent newspaper report stated that two company officials would not face charges.⁸

Later in 2004, Access Cardiosystems, Inc. issued a worldwide recall of approximately 10,000 automated external defibrillators (AEDs).⁹ AEDs are portable devices used to restore normal heart rhythm to patients in cardiac arrest. The problems leading to the recall involved faulty parts that failed to deliver shocks, or in other situations, that resulted in the ON/OFF button becoming inoperative. The company is no longer in business.

This report describes FDA's approval process for medical devices, compares it with the approval process for drugs, and serves as a primer for broader discussions of the impact of various legislative options aimed at maximizing both patient safety and availability of beneficial medical products. For background information about the U.S. drug approval process, see CRS Report RL30989, *The U.S. Drug Approval Process: A Primer*, by Blanchard Randall IV.

Speed of Approval

Thorough evaluation of a new medical product can take a long time. Adverse events are often rare, and they may not become apparent until the product is used in a large number of patients. Large studies are expensive for companies, and long-term follow-up of patients can be difficult as they relocate or change health care providers. In the past, FDA was often criticized for the length of time it took for a new product to get approval. Health care crises, such as the war on cancer and the AIDS epidemic, led to public outcries for faster access to new medicines. Industry claimed FDA was killing or injuring patients by holding up beneficial new medicines. Others were concerned that FDA action was hasty or lenient, bending to pressure from industry.

Congress reacted in several ways. In 1992, the Prescription Drug User Fee Act (PDUFA; P.L. 102-571), which authorized FDA to collect fees for reviewing new drug applications, was enacted. The fees may be used to increase FDA's technical and human resources. PDUFA also established performance goals to reduce approval times. In 1997, the Food and Drug Modernization Act (FDAMA;

⁷ Jeffrey Krasner, "Stents Sold Despite High Failure Rates: Boston Scientific Held Off Recall Amid Alarming Data," *Boston Globe*, Dec. 26, 2004, p. A1.

⁸ Ross Kerber, "Stent Firm Still Target of Federal Inquiry; Boston Scientific Says Two Officials Won't Face Charges," *Boston Globe*, Nov. 13, 2004, p. C1.

⁹ See "Medical Device Recalls, Class 1 Recall: Access CardioSystems Automated External Defibrillators," at [<http://www.fda.gov/cdrh/recalls/recall-110304.html>].

P.L.105-115) gave FDA authority to establish procedures for expediting review of new drugs and devices, with less stringent thresholds of evidence required to demonstrate safety and effectiveness.¹⁰ In 2002, the Medical Device User Fee and Modernization Act (MDUFMA; P.L. 107-250) accomplished for devices what PDUFA did for drugs, authorizing FDA to collect fees for reviewing new device applications and also establishing performance goals for reducing review time.

Postmarket Surveillance System

All of the efforts to decrease the time FDA took to review a new product by easing premarket requirements indeed accelerated product approval time. However, questions remained about the adequacy of FDA's review process in protecting public health, particularly when the modifications to the premarket approval process were not balanced by increased diligence in postmarket surveillance. In a report to Congress in March of 2004, FDA indicated that although companies had agreed to conduct a total of 1,338 post-approval drug studies, 65% of these studies had not begun, and just 33% were on schedule or had been completed. An internal FDA study examining postmarketing requirements for 127 devices approved between 1998 and 2000 found that of 45 approvals that required manufacturers to conduct postmarket review, 10 (or 22%) did not submit the required follow-up results.¹¹

Recent events also raise questions about whether the current postmarket surveillance mechanisms adequately identify unsafe drugs and devices. Are there better mechanisms for identifying unsafe products? For example, FDA requires manufacturers of certain medical devices to develop and maintain a tracking system that will enable them to quickly locate patients using devices once they are commercially available. Supporters of the regulation indicate that tracking information can facilitate notifications and recalls in the event that serious risks become evident. Opponents cite cost and difficulties in following and locating patients over time as barriers to tracking a large number of devices. Some devices, such as laboratory tests, may be almost impossible to track due to the large number of users for high-volume tests. Tracking, as done for devices, is currently not required of any drug; such tracking would likely be difficult to implement given the high volume of drugs prescribed and the difficulty of determining patient compliance. If products are identified as unsafe after marketing, what barriers exist to FDA's ability to correct problems (i.e., by restricting their use after approval or removing them from the market)? Given differences in the way drugs and devices are used, produced, and regulated, should remedies apply evenly across medical products?

¹⁰ Known as the "least burdensome" approach, it mainly reduced the number of controlled studies that constituted "valid scientific evidence" from two to one, and led to the acceptance of surrogate endpoints (laboratory or physical findings associated with disease) rather than clinical outcomes (such as improvement in survival, reduction in morbidity, etc.) as a basis for establishing effectiveness.

¹¹ R. Kerber, "22% of Medical Device Follow-Up Studies Left Undone," *Boston Globe*, Dec. 24, 2004, p. D1.

Off-Label Use. Off-label use occurs when a medical product is used for a condition or in a manner that was not approved by the FDA. It is a routine practice in medicine that healthcare professionals have flexibility in prescribing interventions that best meet the needs of their patients, regardless of the FDA-approved indications described in the label. Off-label use is particularly prevalent in terminal care, such as with cancer interventions. Manufacturers are required to report serious adverse incidents resulting from off-label use, and the FDA can take action (such as ordering labeling changes) to indicate the dangers of off-label use. However, the FDA argues that it would be nearly impossible for either the manufacturer or the FDA to predict and label against all potential off-label uses and issue warnings accordingly.

Following the congressional hearings, the FDA released a statement and plan on November 5, 2004, regarding strengthening its post-approval safety program.¹² Elements include sponsoring a study by the Institute of Medicine (IOM) to assess and make recommendations about improving FDA's drug safety system, especially postmarketing monitoring. IOM is to also examine whether FDA should develop an organizational unit to oversee drug postmarketing safety issues separate from the office that conducts premarket assessments.¹³ These actions focus on drug safety issues, and will not investigate aspects of the device approval process.

Disclosure of Study Results

All drugs and devices carry some risk; none are 100% safe and effective. Part of FDA's responsibility in both pre- and postmarket review is to ensure that the risk is reasonable given the expected benefits for the intended patient population. Each year, approximately 1-2 drugs and 6-8 devices are removed from the market for safety concerns.¹⁴ What makes the cases in 2004 significant is, in part, the notion that FDA and/or the manufacturer failed to disclose data concerning the potential problems in a timely manner, exposing many patients to serious health risks. Questions that Congress may wish to consider include: What is an appropriate balance between the availability of a product and public safety? When do manufacturers or the FDA have a duty to disclose any evidence of a potential problem with a product? Were there signals identified during premarket review of the products discussed above that could have prevented or minimized these cases had postmarket surveillance and disclosure been in effect? Who should determine what is an "acceptable risk" to a patient who may have no other alternative than to use a potentially dangerous drug or device or suffer from their disease or condition?

Under the Adverse Event Reporting (AER) and Medical Device Reporting (MDR) regulations for drugs, biologics, and devices, manufacturers are required to

¹² Food and Drug Administration, *FDA Acts to Strengthen the Safety Program for Marketed Drugs*, FDA Statement, Nov. 5, 2004, at [<http://www.fda.gov/bbs/topics/news/2004/NEW01131.html>].

¹³ "FDA Drug Safety Review Will Weigh Need For A Separate Safety Agency," *The Green Sheet*, Nov. 15, 2004, p. 1.

¹⁴ U.S. General Accounting Office, *Drugs Withdrawn from Market*, Jan. 19, 2001 [GAO-01-286R]; and *Medical Device Recalls: An Overview and Analysis 1983-88*, Aug. 1989 [GAO/PEMD-89-15BR].

report to FDA any serious adverse events associated with use or misuse of their products. At any time they become aware that there is a potential concern with their product, manufacturers can voluntarily notify health professionals and consumers, and/or with FDA approval, change the labeling (written material supplied with the product) to add precautionary or warning language that would improve safe and effective use of their product. Alternatively, FDA can order that the label be changed as soon as there is reasonable evidence that there is an association between the product and a serious hazard.

The difficulty comes with the definition of “reasonable evidence” and the boundaries of “association” with a serious adverse event. Because of the rarity of most adverse events, it is often difficult to determine whether the product or some other unknown factor is causing the event, particularly when the determination is made outside of the controlled environment of a trial. Furthermore, no single trial is likely to identify all possible adverse events. In the case of pediatric antidepressants, the adverse outcome — an increase in suicidal behaviors in young people — was also associated with the condition that the drug was designed to treat: depression. In recent years, the policy has been to err on the side of keeping a product on the market, maintaining patient access for those who do experience clinical benefits.

Financial Conflict of Interest. Several concerns have been raised as to the potential conflicts of interest that may arise when clinical trial investigators, Institutional Review Board (IRB) members (who approve protocols for the conduct of clinical studies), and FDA advisory committee members hold financial interests in the companies whose products are coming before them. With a declining rate of growth in NIH funding for research to examine the safety and effectiveness of a new drug, investigators are often given financial grants or other incentives (e.g., stock options) for participating in the conduct of clinical trials of their products. While FDA regulations require the disclosure of financial information for certain activities (21 CFR Part 54, 21 CFR § 19.10), similar requirements applicable to study investigators seeking to publish trial results or to IRB members are for the most part lacking.

On February 28, 2005, Senator Christopher Dodd introduced S. 470, the Fair Access to Clinical Trials (FACT) Act. This bill is similar to two bills introduced in during the 108th Congress by Representative Edward Markey (H.R. 5252) and Senator Dodd (S. 2933). The legislation seeks to address one aspect of improving drug safety by requiring registration of all clinical trials of all FDA-regulated medical products before the enrollment of human subjects, and the subsequent posting of their results. The legislation would also impose requirements for the disclosure of financial conflicts of interest for investigators.¹⁵ The broad scope of the proposed

¹⁵ Though FDA requires manufacturers to register their clinical trials with the government [<http://www.clinicaltrials.gov>] less than half of trials are registered (see Sharon Vedantam, “Drugmakers Prefer Silence on Test Data,” *Washington Post*, July 6, 2004, p. A1). A centralized repository of clinical trial results does not exist. Medical journals tend to favor publication of trials with positive results, making information from negative or inconclusive trials difficult to find. FDA publishes summaries of safety and effectiveness for approved (continued...)

legislation in the 108th Congress prompted the medical device industry to question whether the remedy, drafted primarily in response to drug safety issues, applied to some or all medical devices. Over time, differences in the nature of the drug and device industries led to development of different models for FDA regulation of these products. As the 109th Congress will likely continue to investigate FDA's proper role in protecting patient safety, it is important that policymakers be aware of these differences, since they may wish to consider them in oversight or legislation. Likewise, it is important to consider the appropriate balance between stringency and leniency in premarket and postmarket review for both drugs and devices so that oversight, legislation, or regulation can offer an optimum level of patient protection without stifling product development or innovation.

History of Device Legislation

Though food has been regulated since early colonial times, and drugs since the Drug Importation Act of 1848, medical devices did not come under federal scrutiny until Congress passed the Federal Food, Drug and Cosmetic Act (FFDC) of 1938 (P.L. 75-717). At that time, few medical devices existed. In 1966, the Fair Packaging and Labeling Act (P.L. 89-755) required all consumer products in interstate commerce to be labeled accurately and truthfully, with FDA enforcing the provisions on regulated medical products, including medical devices.

The Medical Device Amendments of 1976 (MDA; P.L. 94-295) was the first major legislation passed to ensure safety and effectiveness of medical devices, including diagnostic products, before they could be marketed. The amendments required manufacturers to register with FDA and follow quality control procedures in their manufacturing processes. Some products were required to undergo premarket review by FDA, while others had to meet performance standards before marketing. Devices already on the market in 1976 ("preamendment" or "grandfathered" devices) did not have to undergo retrospective approval for marketing. Instead, they were to be broadly classified by FDA into one of three regulatory classes based on the risk they posed to the patient. Devices coming to market after 1976 had to undergo pre-market review (unless they were exempt). Devices could be "cleared" or "approved" by FDA either by demonstrating that they were substantially equivalent to a preamendment device, or if the device (or its use) were truly novel, by demonstrating that it was safe and effective on its own merit.

¹⁵ (...continued)

trials, but does not publish information about products that are not approved (or new uses of approved products), or that are withdrawn by the manufacturer from FDA review. The argument against publication of results for unapproved uses or withdrawn applications for drugs is that the manufacturer may wish, after collecting more data, to resubmit the application. In the device regulations, FDA can disclose non-trade secret information at any time after making a decision as to whether to approve a product; however, they publish only summaries of safety and effectiveness for approved products. Information regarding non-approved or withdrawn applications may be requested under the Freedom of Information Act (FOIA), but the process may be time-consuming. For more information, see CRS Report RS21944, *Clinical Trials Reporting and Publication*, by Erin Williams and Susan Thaul.

In 1990, the Safe Medical Devices Act (SMD Act; P.L. 101-629) established postmarket requirements for medical devices. The SMD Act required facilities that use medical devices to report to FDA any incident that suggested that a medical device could have caused or contributed to the death, serious illness, or injury of a patient. Manufacturers of certain permanently implanted devices were required to establish methods for tracking the patients who received them and to conduct postmarket surveillance to identify adverse events. The act authorized FDA to carry out certain enforcement actions, such as device product recalls, for products that did not comply with the law.

In 1997, the Food and Drug Administration Modernization Act (FDAMA; P.L. 105-115) mandated the most wide-ranging reforms in FDA practice since 1938. For medical devices, provisions included measures to accelerate premarket review of devices and to regulate company advertising of unapproved uses of approved devices.

In 2002, the Medical Device User Fee and Modernization Act (MDUFMA; P.L. 107-250) enacted three significant provisions for medical devices: (1) it established user fees for premarket reviews of devices; (2) it allowed establishment inspections to be conducted by accredited persons (third parties); and (3) it instituted new regulatory requirements for reprocessed single-use devices.¹⁶ The additional funds provided to FDA from user fees are intended to increase FDA's technical and human resources so that statutorily mandated deadlines may be met.

Medical Device Approval Process

Section 201(h) of the FFDC Act (21 USC § 321 (h)) defines a medical device 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 —

- (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
- (2) 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
- (3) 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 its primary intended purposes.

Medical devices that are sold in the United States are regulated by two centers within FDA: the Center for Devices and Radiological Health (CDRH) and the Center for Biologics Evaluation and Research (CBER). CDRH is responsible for regulating firms that manufacture, repack, relabel, and/or import most medical

¹⁶ MDUFMA was amended in 2004 by the Medical Devices Technical Corrections Act (MDTCA; P.L. 108-214) to clarify Congress's intent and to improve and expand upon some features of MDUFMA.

devices, including surgical instruments, implantable devices, diagnostic equipment, clinical laboratory tests, and medical and non-medical radiation emitting electronic products (such as lasers, x-ray systems, ultrasound equipment, microwave ovens, and color televisions). CBER regulates medical devices involved in the collection, processing, testing, manufacture and administration of licensed blood, blood components, and cellular products, including HIV test kits used to screen donor blood and cellular products, and to diagnose, treat, and monitor persons with HIV and AIDS.

Premarket Clearance or Approval

In order to be marketed in the United States, a medical device must comply with certain “controls” to ensure that they are used safely and effectively in the patients for whom they were developed (i.e., the target population). The level of control, and therefore the specific regulations that a manufacturer¹⁷ must follow, are determined by the level of risk that the device poses to patients from its use or misuse. Following the enactment of the MDA of 1976, FDA grouped devices that were already on the market into 16 medical specialties referred to as panels.¹⁸ FDA then established three risk classifications — Class I, II, and III — representing low-, moderate- and high-risk categories. FDA classified in the Code of Federal Regulations (CFR) approximately 1,700 different generic types of devices that were already on the market. After they were classified in the CFR, these pre-1976 devices could potentially serve as comparison devices in the premarket review of devices that were brought to market after 1976.

Definitions. The following definitions are important in understanding the various aspects of the medical device approval process:

Intended Use and Indications for Use. Often used interchangeably, the intended use and indications for use provide the basis for risk classification, and therefore the types of studies that are required to support approval or clearance of the device, and the stringency of regulations with which the manufacturer will have to comply. The intended use statement generally describes the device function or physiological purpose (e.g., removes water from blood, cuts tissue, detects protein in urine) and can include the indications for use (see 21 CFR § 807.92(a)(5)). The indications for use include a general description of the disease or condition that the device will diagnose, treat, prevent, cure, or mitigate (e.g., diabetes, stage III breast cancer), a description of the patient population (e.g., patients with edema, juveniles,

¹⁷ The term “manufacturer” is used throughout this report for simplicity, but also includes any person, organization, or sponsor that submits a marketing application to FDA for marketing approval for a medical device.

¹⁸ The panels are found in 21 CFR Parts 862 through 892. They include clinical chemistry and clinical toxicology devices, hematology and pathology devices; immunology and microbiology devices; anesthesiology devices; cardiovascular devices; dental devices; ear, nose and throat device; gastroenterology-urology devices; general and plastic surgery devices; general hospital and personal use devices; neurological devices; obstetrical and gynecological devices; ophthalmic devices; orthopedic devices; physical medicine devices; and radiology devices.

women), any specific or special clinical circumstances (e.g., patients with blood tumor marker levels greater than 4.0 ng/mL), clinical settings (e.g., clinical laboratory, physician office, hospital), anatomical sites, or any other defining information about how the device will be used (21 CFR § 814.20 (b)(3)(I)).

Predicate Device. The “predicate device” is any device that a manufacturer references to obtain a clearance based on a determination of “substantial equivalence” (see definition below). To be a predicate, the device must have either been on the market before 1976, or it could have been cleared for marketing after 1976, but must have the same intended use as a device classified in the CFR. For example, a device that measures glucose from blood to test for diabetes was sold in 1972. After the MDA of 1976, these devices were determined to be Class II and can be found in the CFR:

21 CFR 862.1345 Glucose test system.

(a) Identification. A glucose test system is a device intended to measure glucose quantitatively in blood and other body fluids. Glucose measurements are used in the diagnosis and treatment of carbohydrate metabolism disorders including diabetes mellitus, neonatal hypoglycemia, and idiopathic hypoglycemia, and of pancreatic islet cell carcinoma.

(b) Classification. Class II.

If a company wants to sell a new device to measure glucose in 2005, it is required to seek FDA clearance. As long as the new device has the same intended use as the older device (i.e., “... intended to measure glucose quantitatively in blood and other body fluids. Glucose measurements are used in the diagnosis and treatment of carbohydrate metabolism disorders including diabetes mellitus, neonatal hypoglycemia, and idiopathic hypoglycemia, and of pancreatic islet cell carcinoma”), the manufacturer of the new device can base its marketing application on data that compares the new device with the old device, rather than conducting a new, large-scale clinical study.

Substantial Equivalence. Substantial equivalence is the standard of approval for most non-exempt (i.e., from premarket review) low- to moderate-risk devices.¹⁹ Substantial equivalence is determined based on a comparison of the performance characteristics of the new device with a predicate device. In making a determination of substantial equivalence, the new device must either have the same intended use and technological characteristics as the predicate device, or have different technological characteristics that do not raise new questions of safety and effectiveness.

The manufacturer decides what predicate device it would like to use in comparison with its new device. However, FDA has the ultimate discretion in determining whether the comparison is appropriate. Devices that are found to be

¹⁹ Many low-risk devices can be deemed “exempt” from premarket review. This means that the manufacturer does not have to file a premarket notification (i.e., a 510(k)) or a premarket application (PMA) with FDA demonstrating that the device is safe and effective. Manufacturers of exempt devices are still required to comply with other regulations, known as general controls.

substantially equivalent to another device receive FDA “clearance” rather than “approval.”

Safe and Effective. Safety and effectiveness is a higher standard than substantial equivalence. The evidence required to meet the standard may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use (21 CFR § 860.7(c)(2)). FDA considers there to be reasonable assurance of safety when it can be determined that the probable benefits to health that result from use of the device as directed by the manufacturer outweigh any probable risks (21 CFR § 860.7(d)(1)). Investigations for safety can include animal studies, human studies, and/or non-clinical *in vitro* studies (21 CFR § 860.7(d)(2)). FDA considers there to be reasonable assurance of effectiveness when, based upon valid scientific evidence, the use of the device in the target population according to the manufacturer’s instructions will provide clinically significant results (21 CFR § 860.7(e)(1)). Valid scientific evidence includes evidence from well-controlled clinical trials, other carefully defined clinical investigations, well-documented case histories, and reports of significant human experience. The evidence can be collected by the manufacturer or a representative, and/or can be abstracted from the medical literature. Devices that meet the standard of “safe and effective” receive FDA “approval.”

Device Classification. Medical devices are classified into a regulatory category based on the risk that is posed to the patient with its use or misuse. A new device can be classified based on comparison with a legally marketed device, by regulation, or by a classification panel. If unsure what classification a product would receive, a manufacturer may make a formal request for classification to FDA, to which FDA must respond within 60 days.

Class I. Devices in Class I are those for which *general controls* (described below) alone are sufficient to ensure safe and effective use of the product (21 CFR § 860.3(c)(1)). Many Class I devices are *exempt* from premarket review by FDA, because FDA previously determined that they present low risk of illness or injury to a patient (see 21 CFR Parts 862 to 892). Although a manufacturer of an exempt device does not have to file a submission containing performance or other data with FDA before marketing the device (as manufacturers of nonexempt devices do), it still has to comply with the remaining general controls.

General controls are the minimum level of regulation that applies to all FDA regulated medical devices.²⁰ Manufacturers:

- are prohibited from selling an adulterated product,²¹

²⁰ FDA, *General Controls for Medical Devices*, Apr. 16, 1998, at [<http://www.fda.gov/cdrh/devadvice/363.html>].

²¹ A device is adulterated if it includes any filthy, putrid, or decomposed substance, or if it is prepared, packed, or held under unsanitary conditions. The FDC Act further states that a device is adulterated if its container contains any poisonous or deleterious substance, or if its strength, purity or quality varies significantly from what the manufacturer claims. For
(continued...)

- are prohibited from misbranding a product,²²
- must register their facility with FDA and list all of the medical devices that they produce or process,
- must file the appropriate premarket submission with the agency at least 90 days before introducing a *non-exempt* device onto the market, and
- must report to FDA any incident that they are aware of that suggests that their device may have caused or contributed to a death or serious injury.

Class II. Devices in Class II are those for which general controls alone are not sufficient to provide reasonable assurance of safety and effectiveness. Class II includes devices that pose a moderate risk to patients, and may include new devices for which information or “special controls” are available that will reduce or mitigate the risk. Most Class II devices require premarket review; however, some are exempt by regulation (21 CFR § 860.3(c)(2)).

Special controls can include any requirement that FDA deems necessary to assure safe and effective use of a medical device: for example, performance standards, postmarket surveillance requirements, patient registries, or the development and dissemination of guidance documents. Special controls guidance documents often contain information for the device manufacturer on FDA’s current thinking of best practices to assure safety and effectiveness of a particular type of device. These include, but are not limited to, guidance on the types of studies that that the manufacturer could perform to support an application for marketing, guidelines about labeling for use in a particular target population, or suggestions for quality control procedures or manufacturing practice.

Class III. Class III medical devices include those for which general and/or special controls are not sufficient to assure safe and effective use of the device. Class III includes devices which are life-supporting or life-sustaining, and devices which present a high or potentially unreasonable risk of illness or injury to a patient. New devices which are not classified as Class I or II by another means, are automatically designated as Class III unless the manufacturer files a request or petition for reclassification under Section 513(f)(2) of the FFDC Act (See also 21 CFR § 860.3(c)(3)).

FDAMA gave FDA the authority to establish procedures for meeting with manufacturers prior to preparing a submission.²³ The procedures aim to speed the

²¹ (...continued)

higher class devices, a device can be considered adulterated if it fails to meet performance requirements outlined in its approval, or if it is in violation of other Good Manufacturing Practice requirements.

²² A device is misbranded when all or part of the labeling (i.e., the FDA-approved printed material providing information about the device) is false, misleading, or missing.

²³ For guidance on the procedures established, see *Early Collaboration Meetings Under the FDA Modernization Act*; Final Guidance for Industry and CDRH Staff, Feb. 28, 2001, at (continued...)

review process by giving FDA and a manufacturer the opportunity to address questions and concerns about the device and/or the planned studies that will be used to support the marketing application before the studies are initiated and the application is submitted. For example, the “pre-IDE” process is an informal “pre-submission” process. The “pre-IDE” process is so-called in name only; submitting a pre-IDE does not mean that manufacturers are required to submit subsequently an investigational device exemption (IDE) application.²⁴ The pre-IDE process is simply a means for FDA and industry to engage in dialogue about a new device, before a study is initiated or a marketing application is submitted. The pre-IDE process may involve sending analytical or clinical protocols to FDA for review and comment before proceeding with studies, or meeting with FDA to discuss protocols and/or possible regulatory pathways. This particular process is strictly voluntary, and not binding on either FDA or industry. The benefits to manufacturers include an opportunity to begin a dialogue with FDA, to promote greater understanding of new technologies, to reduce the cost of research studies by focusing on the important information needed for FDA approval (or clearance), eliminating unnecessary or burdensome studies, and to speed the review process for the future marketing application since FDA will already be familiar with the device.

Marketing Applications for Medical Devices. Prior to marketing a medical device in the United States, a manufacturer must register their facility with the FDA and list the devices that they commercialize. The classification of the device (Class I, II or III based on the risk posed to the patient) determines whether or not a premarket submission is required, and if so, what type of submission is required. The following sections describe the types of premarket submissions that FDA reviews for medical devices.

Premarket Notification (510(k)). A 510(k) submission is required for any new, non-exempt low- or moderate-risk medical device that will be marketed in the United States. The standard for clearance of a traditional 510(k) is substantial equivalence with a predicate device. Though usually for Class I or II devices, an older, preamendment Class III device may sometimes use a 510(k) submission. A 510(k) could also be used for currently marketed devices for which the manufacturer seeks a new indication (e.g., a new population, such as pediatric use, or a new disease or condition), or for which the manufacturer has changed the design or technical characteristics such that the change may affect the performance characteristics of the device.

There are several types of 510(k)s: traditional, abbreviated, special and *de novo*. In a traditional 510(k), the manufacturer submits information about the performance of the device under specific conditions of use. It also contains information about the design of the device, characteristics of device components, representations of packaging and labeling, a description and summary of the non-clinical and clinical studies that were done to support the device performance characteristics, a

²³ (...continued)

[<http://www.fda.gov/cdrh/ode/guidance/310.pdf>].

²⁴ For more information on the IDE, please refer to the “Marketing Applications” section that immediately follows this discussion.

description of means by which users can assess the quality of the device, and information about any computer software or additional or special equipment needed. Several administrative forms are also required.²⁵ Most of the studies supporting a 510(k) submission are not true clinical studies. While FDA prefers to see data on performance of the device in the actual intended population, substantial equivalence in many cases, means only that the device performs in a similar fashion to the predicate under a similar set of circumstances. As a result, many devices never have to demonstrate safety and effectiveness through clinical studies.

FDA may take any of the following actions on a 510(k) after conducting its review (21 CFR § 807.100(a)): find the device substantially equivalent to the predicate and issue a clearance letter, find the device not substantially equivalent (NSE) and issue an NSE letter prohibiting marketing, or request additional information (with the final clearance decision pending review of that information). A manufacturer generally has 30 days to provide any additional information, or the FDA may issue a notice of withdrawal of the application (21 CFR § 807.87(l)). The manufacturer may, at any time, withdraw its 510(k). FDA has 90 days to review a traditional 510(k).²⁶

Abbreviated and special 510(k)s were new approaches to premarket notification that came from FDAMA of 1997, intended to streamline and expedite FDA's review for routine submissions meeting certain qualifications, thus leaving more reviewer time for more complicated submissions. An abbreviated 510(k) uses guidance documents developed by FDA to communicate regulatory and scientific expectations to industry. Guidance documents have been prepared for many different kinds of devices, and are available on FDA's website. All guidance documents are developed in accordance with Good Guidance Practices (GGP, 21 CFR § 10.115)), and many with public participation or opportunities for public comment.²⁷ In addition, FDA can either develop performance or consensus standards or 'recognize' those developed by outside parties (21 CFR Part 861). In an abbreviated 510(k), the manufacturer describes what guidance document, special control, or performance standard was used, and how it was used to assess performance of their device. Other minimum required elements are the product description, representative labeling, and a summary of the performance characteristics. FDA typically reviews an abbreviated 510(k) in 60 days.

The Quality System Regulation (QSR; 21 CFR § 820.30) is the regulation that describes the good manufacturing practice (GMP) requirements for medical devices (see the Manufacturing section of this report for more detail on QSR). A special

²⁵ FDA, "Content of a 510(k)," June 30, 2003, at [<http://www.fda.gov/cdrh/devadvice/314312.html>], and *How to Prepare a Traditional 510(k)*, Jan. 4, 2005, at [http://www.fda.gov/cdrh/devadvice/3143.html#link_4].

²⁶ The FDA time clock (i.e., review cycle) begins when FDA receives the 510(k) and ends with the date that FDA issues either a request for additional information or a decision. More than one cycle may occur before FDA issues its final decision.

²⁷ FDA continually accepts public comment on any draft or final guidance document.

510(k) utilizes the design control²⁸ requirement of the QSR and may be used for a modification to a device that has already been cleared. The modifications should not affect the safety and effectiveness of the device. The special 510(k) allows the manufacturer to declare conformance to design controls, without providing the data. This type of submission references the original 510(k) number, and contains information about the design control requirements. FDA aims to review most special 510(k)s in 30 days.

Under the FFDC Act, first-of-a-kind devices lacking a legally marketed predicate would automatically be designated Class III. FDAMA amended Section 513(f) to allow FDA to establish a new, expedited mechanism for reclassifying these devices based on risk, thus reducing the regulatory burden on manufacturers. The *de novo* 510(k), though requiring more data than a traditional 510(k), often requires less information than a premarket application (PMA).

In a *de novo* 510(k) process, the manufacturer submits a traditional 510(k) for its device. However, because there is no predicate device or classification, the agency will return a decision of not substantially equivalent. Within 30 days, the manufacturer submits a petition requesting reclassification of its device into Class II or I, as appropriate. Within 60 days, FDA will render a decision classifying the device according to criteria in 513(a)(1) of FFDC Act. With approval, the FDA issues a regulation that classifies the device. If the device is Class II, a special controls guidance document is also developed that then allows subsequent manufacturers to submit either traditional or abbreviated 510(k)s.²⁹

In 2002, the MDUFMA authorized FDA to charge a fee for premarket reviews, including non-exempt, non-waived 510(k)s. For FY2005, the standard fee is \$3,502 and \$2,802 for small businesses. FDA will not file an application unless the fee is paid at the time of submission.

Premarket Application (PMA). A PMA is the most stringent type of device marketing application required by FDA for new and/or high-risk devices. PMA approval is based on a determination by FDA that the application contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s) (21 CFR Part 814). A PMA will contain the following information (amongst other things): administrative requirements, summaries of non-clinical and clinical data supporting the intended use and performance characteristics, detailed information on the design of the device and a description of the device components, instructions for use, representations of packaging and labeling, a description of means

²⁸ Design controls are a series of pre-determined checks, verifications, and specifications that are built into the manufacturing process to validate the quality of the product throughout the process. These can include: defining the personnel responsible for implementing steps in the development and manufacturing process, defining specifications and standards for assessing the quality of the materials that go into making the product, designing specifications for accepting and rejecting different batches or lots of final product, requirements for maintaining appropriate records, etc.

²⁹ Guidance for Industry and FDA Staff, New Section 513(f)(2) — *Evaluation of Automatic Class III Designation*, Feb. 19, 1998, at [<http://www.fda.gov/cdrh/modact/clasiii.pdf>].

by which users can assess the quality of the device, information about any computer software or additional or special equipment needed, literature about the disease and the similar devices, information on the manufacturing process, and assurance of compliance with QSR. In contrast to a 510(k), PMAs generally require some clinical data, but can also use studies from the medical literature (a “paper PMA”). Approval is based not only on the strength of the scientific data, but also on inspection of the manufacturing facility to assure that the facility and the manufacturing process are in compliance with the quality systems regulations (QSR: 21 CFR Part 820). FDAMA made it easier for manufacturers to submit the required sections of a PMA in a serial fashion as data are available (“modular PMA”).

When a PMA is first received, FDA has 45 days to make sure the application is administratively complete. If so, the FDA formally files the application. If not, the application is returned. FDA then has 75 days to complete the initial review and determine whether an advisory panel meeting will be necessary. Advisory committees, comprised of scientific, medical, and statistical experts, and industry and consumer representatives, can be convened to make recommendations on any scientific or policy matter before FDA. They allow for interested persons to present information and views at an oral public hearing before the advisory committee (21 CFR Part 14). FDA typically accepts advisory committee recommendations for an application (approvable, approvable with conditions or non-approvable); however, there have been cases where the decision has not been consistent with the recommendation (e.g., where the conditions for approval are so burdensome as to practically present a non-approvable situation). CDRH will hold joint advisory committee meetings with other centers where necessary. After FDA notifies the applicant that the PMA has been approved or denied, a notice may be published on the Internet (1) announcing the data on which the decision is based, and (2) providing interested persons an opportunity to petition FDA within 30 days for reconsideration of the decision.

Though FDA regulations allow 180 days to review the PMA and make a determination (21 CFR § 814.40), in reality the review time could be much longer. MDUFMA established performance goals to reduce the review time for PMAs.³⁰ The FY2005 fees have been set at \$239,237 for a standard PMA (\$90,910 for small business).

510(k), and PMA Supplements. Once a device has been cleared through a 510(k) process or approved through the PMA process, the manufacturer can market the device only for the intended use that the FDA cleared or approved. For example, a device, such as a stent, approved to treat coronary artery disease may not be marketed for treatment of blocked biliary ducts unless the manufacturer files additional information with FDA to demonstrate that the device is safe and effective for the new use. The information can be filed as a supplement to the original application. Supplements are required not only for new uses of a cleared or approved device, but also for design or manufacturing changes that may impact safety and

³⁰ “FDA Announces New Goal for Reducing Total Device Review Times,” *FDA News*, Aug. 5, 2003, at [<http://www.fda.gov/bbs/topics/NEWS/2003/NEW00929.html>].

effectiveness (e.g., changing the type of metal or plastic on a device, using a different antibody for diagnosis of a disease, etc.).

Fees for 510(k) supplements are the same as for the original application. If a PMA supplement contains controversial or new information, it may be subject to advisory committee review just like an original application. In that case, the user fees are the same as the original. User fees to review other supplements are: \$51,436 for a traditional PMA supplement with a 180-day review time (\$19,546 small business), and \$17,225 for a real-time supplement (\$6,546 for small business).³¹

Investigational Device Exemption (IDE). An IDE allows an unapproved device (most commonly an invasive or life-sustaining device) to be used in a clinical study to collect data required to support a submission, most commonly a PMA, at some later point in time.³² Investigational use can also include clinical evaluation of certain modifications to or new intended uses of legally marketed devices (e.g., supplemental application). All clinical evaluations of investigational devices, unless they are exempt, must have an IDE and be approved by an IRB, before the study is initiated. The IDE permits a device to be shipped lawfully for investigation of the device without requiring that the manufacturer comply with other requirements of the FFDC Act, such as registration and listing. Manufacturers of devices with IDE's are also exempt from the quality systems regulations (QSR), except for the requirements for design control.

While under investigation, manufacturers, sponsors, clinical investigators and IRBs must comply with Good Clinical Practices, including all regulations that govern the conduct of clinical studies:

- Investigational Device Exemptions (21 CFR Part 812) covering the procedures for the conduct of clinical studies with medical devices including application, responsibilities of sponsors and investigators, labeling, records, and reports;
- Protection of Human Subjects (21 CFR Part 50) providing the requirements and general elements of informed consent;
- Institutional Review Boards (21 CFR Part 56) covering the procedures and responsibilities for institutional review boards (IRBs) that approve clinical investigations protocols;
- Financial Disclosure by Clinical Investigators (21 CFR Part 54) covering the disclosure of financial compensation to clinical investigators which is part of FDA's assessment of the reliability of the clinical data; and

³¹ A "real time" supplement is "a supplement to an approved PMA or premarket report under Section 515 of the FFDC Act that requests a minor change to the device, such as a minor change to the design of the device, software, manufacturing, sterilization, or labeling, and for which the applicant has requested and the agency has granted a meeting or similar forum to jointly review and determine the status of the supplement." The review time is generally quicker (because the change is minor) compared to other types of supplements.

³² FDA, *IDE Overview*, July 8, 2003, at [<http://www.fda.gov/cdrh/devadvice/ide/index.shtml>].

- Design Controls of the QSR (21 CFR Part 820 Subpart C) providing the requirement for procedures to control the design of the device in order to ensure that the specified design requirements are met.

Devices are exempt from IDE requirements when: testing is noninvasive, testing does not require invasive sampling, testing does not introduce energy into a subject, testing is not stand alone (i.e., is not used for diagnosis without confirmation by other methods or medically established procedure) (21 CFR § 812.2(c)(3)).

Humanitarian Device Exemption (HDE). An HDE is an application that is similar to a PMA, but exempt from the effectiveness requirements. An approved HDE authorizes marketing of a humanitarian use device. A humanitarian use device is intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect fewer than 4,000 individuals in the U.S. per year.

Before submitting an HDE application, the manufacturer submits a request for a humanitarian use device designation to FDA's Office of Orphan Products Development (OOPD). The request includes: (1) a statement that they are requesting a humanitarian use device designation for a rare disease or condition, (2) the name and address of the manufacturer, (3) a description of the rare disease or condition for which the device is to be used, (4) a description of the device, and (5) documentation, with appended authoritative references, to demonstrate that the device is designed to treat or diagnose a disease or condition that affects or is manifested in fewer than 4,000 people in the United States per year (see 21 CFR § 814.102(a)). In order for a device to receive marketing approval under this regulation, there should not be another legally marketed device available to treat or diagnose the disease or condition. Once a device with the same intended use as the humanitarian use device is approved or cleared, an HDE cannot be granted for the humanitarian use device.

The agency has 75 days from the date of receipt to review an HDE application. This includes a 30-day filing period during which the agency determines whether the HDE application is sufficiently complete to permit substantive review. FDA does require that a manufacturer comply with the QSR that the agency deems most relevant to the safety of the device. Alternatively, the manufacturer can request an exemption. Supplements, and sometimes even a new HDE, are required for additional indications.³³

Table 1 shows the number of marketing applications that CDRH received, approved and denied in 2003. Very few applications are actually denied approval. Instead, an application may be deemed "not approvable" in its current form (i.e., typically because the data that the manufacturer provides are not sufficient to demonstrate safety and effectiveness). Applications that are "not approvable" are usually withdrawn by the manufacturer before a denial is rendered.

³³ CDRH, FDA, *Humanitarian Device Exemptions Regulation: Questions and Answers; Final Guidance for Industry*, July 12, 2001, at [<http://www.fda.gov/cdrh/ode/guidance/1381.html>].

Table 1. Number of Marketing Applications for Medical Devices Received, Approved and Denied by CDRH in 2003

Number of applications	CDRH
Received	
Original PMA	54
PMA Supplements	669
510(k)	4,247
Original IDE	242
Original HDE	10
Completed^a	
Original PMA	31
PMA Supplements	494
510(k)	4,132
Original IDE	246
Original HDE	2
Approvals + Approvable (number of decisions made)^b	
Original PMA	31 + 16 (57)
PMA Supplements	494 + 94 (635)
510(k): decision is substantially equivalent	3,522 (4,132)
Original IDE: “approvable” not a valid decision	146 (246)
Original HDE	2 + 0 (2)
Denials + Not Approvable (Number of Decisions)	
Original PMA	0 + 10 (57)
PMA Supplements	0 + 47 (635)
510(k): decision is not substantially equivalent	88 (4,132)
Original IDE: “not approvable” not a valid decision	78 (246)
Original HDE	0 + 0 (2)

Source: ODE and OIVD, *Annual Report: Fiscal Year 2003*, at [<http://www.fda.gov/cdrh/annual/fy2003/ode/2003.pdf>].

- a. The number completed is different than the number received because some applications were received in 2002 and completed in 2003, others received in 2003 may not have been completed in that year.
- b. The number of decisions made can be greater than the number of applications completed because in FDA accounting, an application could have more than one decision. For example, it could have been “approvable” early in the year and later “approved.” An approval means that a product can be marketed, approvable means that the manufacturer had to meet certain conditions before the device could be marketed. Presumably, many applications that are determined to be “not approvable” are subsequently withdrawn from FDA consideration by the manufacturer prior to receiving the denial.

***In vitro* Diagnostic products (IVD).** IVD products are “... those reagents, instruments, and systems intended for use in diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body (21 CFR

§ 809.3). IVDs are medical devices as defined in Section 210(h) of the FFDC Act, and may also be biological products subject to Section 351 of the Public Health Service Act. IVDs are different from other medical devices in that they do not act directly on a patient to produce a result like an implantable, life-sustaining or other device does. Instead, the risk to the patient is from the generation of inaccurate test results (i.e., wrong answers) that lead to mismanagement of a patient's condition.

IVDs (e.g., laboratory tests) may consist of general purpose reagents,³⁴ analyte specific reagents,³⁵ general purpose or specific equipment, sometimes with computer analysis software. Most stand-alone items of general purpose equipment, such as automated clinical analyzers, are exempt Class I devices. However, if the equipment performs a specific test, equipment plus the test becomes a test system. Test systems are considered combination devices, and they are classified according to the risk level of the highest of the two device classifications (i.e., an analyzer may be Class I exempt, but if a manufacturer wishes to market it with an HIV test kit, the system could be regulated as a Class III device and require a PMA). Most IVD products are reviewed in CDRH's Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD), and CBER's Office of Blood Research and Review (OBRR). The classification of existing IVDs can be found in 21 CFR Part 862, 21 CFR Part 864, and 21 CFR Part 866.

Like other medical devices, IVDs are subject to premarket and postmarket controls. IVDs are also subject to the Clinical Laboratory Improvement Amendments (CLIA) of 1988.³⁶ CLIA establishes quality standards for laboratory testing and an accreditation program for clinical laboratories that perform testing using IVD products. CLIA requirements vary according to the technical complexity in the testing process and risk of harm in reporting erroneous results. The regulations establish three categories of testing on the basis of the complexity of the testing methodology: (a) waived tests, (b) tests of moderate complexity, and (c) tests of high complexity. Manufacturers apply for CLIA categorization (determined by FDA) during the premarket process. Under CLIA, laboratories performing only waived tests are subject to minimal regulation. Laboratories performing moderate or high complexity tests are subject to specific laboratory standards governing certification, personnel, proficiency testing, patient test management, quality assurance, quality control, and inspections.

³⁴ A general purpose reagent is "a chemical reagent that has general laboratory application, is used to collect, prepare, and examine specimens from the human body for diagnostic purposes, and is not labeled or otherwise intended for a specific diagnostic application ... [General purpose reagents] do not include laboratory machinery, automated or powered systems (21 CFR § 864.4010)."

³⁵ Analyte specific reagents (ASRs) are "antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents which, through specific binding or chemical reaction with substances in a specimen, are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens (21 CFR § 864.4020(a))."

³⁶ FDA, *Overview of IVD Regulation*, Mar. 4, 2003, at [<http://www.fda.gov/cdrh/oivd/regulatory-overview.html#1>].

CLIA categorization (defining regulatory requirements on the laboratory testing process) do not always match FDA classification (defining regulatory requirements on the tests kits or systems themselves). For example, a “waived” test under CLIA is the simplest test to perform (usually by an untrained user), with the smallest margin of error. As such, they receive little to no oversight under CLIA. However, FDA may designate such a test as Class III, so that it undergoes rigorous review to insure that it performs as advertised (i.e., with a small margin of error in the hands of an untrained user). Most IVDs are exempt from IDE requirements.

Because the benefits and risks to the patient from use of IVDs are indirect (i.e., due to the use of the test result in patient management), FDA requires that the companies demonstrate analytical test performance in patient samples that would test along the continuum of positive and negative for the marker of interest. In addition, FDA requires support for the clinical validity of the test (i.e., evidence that the biological marker that the test is detecting actually is associated with the disease or condition that the company wishes to market the test for in a predictable way). For the many applications seeking clearance for an IVD, biological markers that the test purports to measure may be relatively well characterized with respect to a disease and patient population (such as the link between glucose measurement and diabetes). In these cases, analytical studies using clinically derived samples (e.g., blood specimens from healthy and diabetic individuals) suffice to show that the test is actually detecting the marker. Sometimes, clinical samples can be supplemented by carefully selected artificial samples, particularly if a disease, condition or marker is rare. For example, if FDA were to review a genetic test to measure genetic markers for drug metabolism, they may require the manufacturer to use actual patient samples to demonstrate that they can detect common markers. FDA may, however, allow the company to use artificial or ‘spiked’ samples to test for rare markers so that the company would not have to test an overly burdensome number of clinical samples. In this type of submission, the manufacturer could use medical literature to support the clinical validity of the biological marker to the disease, and would not have to conduct a clinical study to demonstrate that the test measures the marker and the marker is associated with the disease.

For other IVDs, the link between analytical performance of the test in its ability to detect a biological marker and the clinical validity of the marker is not well defined. In these circumstances, new clinical information may be required. FDA rarely requires prospective clinical studies for IVDs, but regularly requests clinical samples with sufficient laboratory and/or clinical characterization to allow an assessment of the clinical validity of a new device. For example, a company seeking to market a test for a new tumor marker may use well-characterized, archived patient samples collected as part of a completely separate study to demonstrate that their test can classify patients in a predictable way. Clinical performance is usually expressed in terms of clinical sensitivity and clinical specificity (when compared to a disease or health state) or agreement (when compared to performance of a predicate device or reference method). For most PMAs, manufacturers identify surrogate endpoints (such as tumor shrinking or reduction in a tumor marker) and establish the device performance in relation to those rather than to disease outcome (such as improved survival).

Post-Approval Requirements and Issues

Once approved or cleared for marketing, manufacturers of medical devices must comply with regulations on labeling and advertising, on production of their device, and on postmarket surveillance of adverse events associated with the use of their device.

Labeling. Like drugs and biological products, all FDA approved or cleared medical devices are required to be labeled in a way that informs a user of how to use the device in a safe and effective manner. Section 201(k) of the FFDC Act defines a “label” as a: “display of written, printed, or graphic matter upon the immediate container of any article.” Section 201(m) defines “labeling” as: “all labels and other written, printed, or graphic matter upon any article or any of its containers or wrappers, or accompanying such article” at any time while a device is held for sale after shipment or delivery for shipment in interstate commerce. The term “accompanying” is interpreted to mean more than physical association with the product; it extends to posters, tags, pamphlets, circulars, booklets, brochures, instruction books, direction sheets, fillers, webpages, etc. “Accompanying can also include labeling that is connected with the device after shipment or delivery for shipment in interstate commerce. According to an appellate court decision “Most, if not all advertising, is labeling. The term ‘labeling’ is defined in the FFDC Act as including all printed matter accompanying any article. Congress did not, and we cannot, exclude from the definition printed matter which constitutes advertising.”

Labeling regulations pertaining to medical devices are found in the following parts of Title 21 CFR:

- General Device Labeling (21 CFR Part 801)
- In Vitro Diagnostic Products (21 CFR Part 809)
- Investigational Device Exemptions (21 CFR Part 812)
- Good Manufacturing Practices (21 CFR Part 820)
- General Electronic Products (21 CFR Part 1010)

All devices must conform to the general labeling requirements. Certain devices³⁷ require specific labeling which may include not only package labeling, but informational literature, patient release forms, performance testing, and/or specific tolerances or prohibitions on certain ingredients.

Various sections of the QSR have an impact on labeling: Section 21 CFR § 820.80(b) requires the inspection and testing of incoming materials including labeling; and 21 CFR § 820.70(f) requires buildings to be of suitable design and have sufficient space for packaging and labeling operations; 21 CFR § 820.120 deals with specific requirements for the control of labeling. This regulation applies to the

³⁷ 21 CFR §§ 801.405 to 801.437. Denture repair kits, impact resistant lenses in sunglasses and eyeglasses, ozone emission levels, chlorofluorocarbon propellants, hearing aids, menstrual tampons, chlorofluorocarbons or other ozone depleting substances, latex condoms, and devices containing natural rubber.

application of labeling to ensure legibility under normal conditions of use over the expected life of the device; and also applies to inspection, handling, storage, and distribution of labeling. FDA considers a device to be adulterated if these requirements are not met. These requirements do not apply to the adequacy of labeling content, except to make sure the content meets labeling specifications contained in the device master record. However, failure to comply with GMP requirements, such as proofreading and change control, could result in labeling content errors. In such cases, the device could be misbranded and/or adulterated.

Manufacturing. Like drugs and devices, medical device manufacturers must produce their devices in accordance with Good Manufacturing Practice (GMP). The GMP requirements for devices are described in the QSR, (Section 520 of the FFDC Act; Part 820 of 21 CFR). The QSRs require that domestic or foreign manufacturers have a quality system for the design, manufacture, packaging, labeling, storage, installation, and servicing of non-exempt finished medical devices intended for commercial distribution in the United States. The regulation requires that various specifications and controls be established for devices; that devices be designed and manufactured under a quality system to meet these specifications; that finished devices meet these specifications; that devices be correctly installed, checked and serviced; that quality data be analyzed to identify and correct quality problems; and that complaints be processed. FDA monitors device problem data and inspects the operations and records of device developers and manufacturers to determine compliance with the GMP requirements.³⁸

Though FDA has identified in QSR the essential elements that a quality system should have, manufacturers have a great deal of leeway to design quality systems that best cover nuances of their devices and the means of producing them.

Postmarket Surveillance. Once their device is approved or cleared, manufacturers must conduct postmarket surveillance studies to gather safety and efficacy data for certain devices introduced into interstate commerce after January 1, 1991. This requirement applies to devices that:

- are permanent implants, the failure of which may cause serious adverse health consequences or death;
- are intended for use in supporting or sustaining human life; or
- present a potential serious risk to human health.

FDA may require postmarket surveillance for other devices if deemed necessary to protect the public health. The primary objective of postmarket surveillance is to study the performance of the device after clearance or approval as it is used in the population for which it is intended — and to discover cases of device failure and its attendant impact on the patient.

Manufacturers may receive notification that their device is subject to postmarket surveillance when FDA files (i.e., accepts) the submission, and again when a final

³⁸ FDA, *Good Manufacturing Practice/Quality Systems*, at [<http://www.fda.gov/cdrh/cmp/gmp.html>].

decision is made. If notified, manufacturers must submit a plan for postmarket surveillance to FDA for approval within 30 days of introducing their device into interstate commerce.

MDUFMA authorized additional appropriations for postmarket surveillance — \$3 million for FY2003, \$6 million for FY2004, and “such sums as may be necessary” in subsequent years. For FDA to receive these resources in subsequent years, it must submit to Congress by January 10, 2007, a study of:

- the effect of medical device user fees on its ability to conduct postmarket surveillance;
- the extent to which device companies comply with postmarket surveillance requirements;
- any improvements needed for adequate postmarket surveillance, and the amount of funds needed to do so;
- recommendations as to whether, and in what amount, user fees should be used for postmarket surveillance, if extended beyond FY2007.³⁹

Adverse Event Reporting. Section 519(a) of the FFDC Act as amended by the SMDA of 1990 required FDA to establish a system for monitoring and tracking serious adverse events that resulted from the use or misuse of medical devices. The Medical Device Reporting (MDR) regulation is the mechanism that FDA and manufacturers use to identify and monitor significant adverse events involving medical devices, so that problems are detected and corrected in a timely manner. User facilities (e.g., hospitals, nursing homes, clinical laboratories) are required to report suspected medical device related deaths to both the FDA and the manufacturers within 10 working days. User facilities may report medical device related serious injuries only to the manufacturer within 10 days. Manufacturers must file a summary of all medical device reports to FDA within 30 calendar days. User facilities must file a summary report annually. Although the FFDC Act gives FDA the authority to impose legal sanctions for not complying with MDR, FDA relies largely on the goodwill and cooperation of all affected groups to accomplish the objectives of the regulation. The searchable MDR database for devices is publically accessible at [<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmdr/search.CFM>].

Medical Device Tracking. Manufacturers must adopt a method of tracking certain devices. These are devices:

- whose failure would be reasonably likely to have serious, adverse health consequences; or
- which are intended to be implanted in the human body for more than one year; or
- which are life-sustaining or life-supporting devices used outside of a device user facility (21 CFR Part 821).

³⁹ FDA, *The Medical Device User Fee and Modernization Act of 2002* — “FAQs,” Aug. 1, 2003, at [<http://www.fda.gov/cdrh/mdufma/faqs.html#postmarket>].

The purpose of device tracking is to ensure that manufacturers of these devices can locate them quickly once in commercial distribution if needed to facilitate notifications and recalls in the case of serious risks to health presented by the devices.⁴⁰ A current list of the devices for which tracking is required can be found at [<http://www.fda.gov/cdrh/devadvice/353.html>].

Compliance and Enforcement. Compliance requirements apply to both the premarket approval process and postmarket surveillance. When a problem arises with a product regulated by FDA, the agency can take a number of actions to protect the public health. Initially, the agency tries to work with the manufacturer to correct the problem on a voluntary basis. If that fails, legal remedies may be taken, such as: asking the manufacturer to recall a product, having federal marshals seize products, or detaining imports at the port of entry until problems are corrected. If warranted, FDA can ask the courts to issue injunctions or prosecute individual company officers that deliberately violate the law. When warranted, criminal penalties, including prison sentences, may be sought.

Each center has an Office of Compliance (OC) which ensures compliance with regulations while pre- or postmarket studies are being undertaken, with manufacturing requirements, and with labeling requirements. The objectives of CDRH's OC's Bioresearch Monitoring (BIMO) program are to ensure the quality and integrity of data and information submitted in support of IDE, PMA, and 510(k) submissions and to ensure that human subjects taking part in investigations are protected from undue hazard or risk. This is achieved through audits of clinical data contained in PMAs prior to approval, data audits of IDE and 510(k) submissions, inspections of IRBs and nonclinical laboratories, and enforcement of the prohibitions against promotion, marketing, or commercialization of investigational devices. Any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept, can be subject to inspection.

The OC also reviews the quality system design and manufacturing information in the PMA submission. It is to determine whether the manufacturer has described the processes in sufficient detail and make a preliminary determination of whether the manufacturer meets the QSR. If the manufacturer has provided an adequate description of the design and manufacturing process, a preapproval inspection can be initiated. Inspection is to include an assessment of the manufacturer's capability to design and manufacture the device as claimed in the PMA and confirm that the quality system is in compliance with the QSR. Postapproval inspections can be conducted within eight to twelve months of approval of the PMA submission. The inspection is to primarily focus on any changes that may have been made in the device design, manufacturing process, or quality systems.

⁴⁰ OIVD, which reviews clinical laboratory test kits and equipment, has the capacity for both premarket scientific review and pre — and postmarket compliance activity.

The compliance offices work closely with the Office of Regulatory Affairs (ORA),⁴¹ which operates in the field to regulate almost 124,000 business establishments that annually produce, warehouse, import and transport \$1 trillion worth of medical products. Consumer safety officers (CSOs) and inspectors typically have conducted about 22,000 domestic and foreign inspections a year to ensure that regulated products meet the agency's standards. CSOs also monitor clinical trials. Scientists in ORA's 13 laboratories typically have analyzed more than 41,000 product samples each year to determine their adherence to the FDA's standards.

Section 516 of the FFDC Act gives FDA the authority to ban devices that present substantial deception or unreasonable and substantial risk of illness or injury. Section 518 enables FDA to require manufacturers or other appropriate individuals to notify all health professionals who prescribe or use the device and any other person (including manufacturers, importers, distributors, retailers, and device users) of any health risks resulting from the use of a violative device, so that these risks may be reduced or eliminated. This section also gives consumers a procedure for economic redress when they have been sold defective medical devices that present unreasonable risks. Section 519 of the Act authorized the FDA to promulgate regulations requiring manufacturers, importers, and distributors of devices to maintain records and reports to assure that devices are not adulterated or misbranded. Section 520(e) of the MDA, authorized FDA to restrict the sale, distribution, or use of a device if there cannot otherwise be reasonable assurance of its safety and effectiveness. A restricted device can only be sold on oral or written authorization by a licensed practitioner or under conditions specified by regulation.

Warning Letter. A warning letter is a written communication from FDA notifying a responsible individual, manufacturer, or facility that the agency considers one or more products, practices, processes, or other activities to be in violation of the laws that FDA enforces. The warning letter informs the recipient that failure to take appropriate and prompt action to correct and prevent any future repeat of the violations could result in an administrative or regulatory action. Although serious noncompliance is often a catalyst for issuance of a warning letter, the warning letter is informal and advisory. Warning letters are publically available on FDA's website at [<http://www.fda.gov/foi/warning.htm>].

Product Recall. A recall is a method of removing or correcting products that FDA considers are in violation of the law.⁴² Medical device recalls are usually conducted voluntarily by the manufacturer (21 CFR Part 7), after negotiation with the FDA. Under 21 CFR Part 806, manufacturers (including refurbishers and reconditioners) and importers are required to report to FDA any correction or removal of a medical device that is undertaken to reduce a health risk posed by the device. A recall may be a total market withdrawal or may be of a portion of product

⁴¹ See ORA at [<http://www.fda.gov/ora/>].

⁴² Recall does not include market withdrawal or a stock recovery. A market withdrawal is a firm's removal or correction of a distributed product for a minor violation that does not violate the law and would not be subject to legal action by the FDA, e.g., normal stock rotation practices, routine equipment adjustments and repairs, etc. Stock recovery involves correction of a problem before product is shipped (i.e., is still in the manufacturer's control).

(such as a single lot). In rare instances, where the manufacturer or importer fails to voluntarily recall a device that is a risk to health, FDA may issue a recall order to the manufacturer (21 CFR Part 810).

When a recall is initiated, FDA performs an evaluation of the health hazard presented taking into account the following factors, among others:

- Whether any disease or injuries have already occurred from the use of the product;
- Whether any existing conditions could contribute to a clinical situation that could expose humans or animals to a health hazard;
- Assessment of hazard to various segments of the population, (e.g., children, surgical patients, pets, livestock, etc.), who would be exposed to the product;
- Assessment of the degree of seriousness of the health hazard to which the populations at risk would be exposed;
- Assessment of the likelihood of occurrence of the hazard;
- Assessment of the consequences (immediate or long-range) of occurrence of the hazard.

Following the health hazard assessment, FDA assigns the recall a classification according to the relative degree of health hazard. *Class I* recalls are the most serious, reserved for situations where there is a reasonable probability that the use of, or exposure to, a product will cause serious adverse health consequences or death. *Class II* recalls are for situations where the use of, or exposure to, a product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote. In a *Class III* recall situation, the use of, or exposure to, a product is not likely to cause adverse health consequences.

In addition to a warning letter or recall, FDA may also issue a public notification or safety alert (e.g., “Dear Doctor” letter), to warn healthcare providers and consumers of the risk of the device in question. The main page for recalls, market withdrawals, and safety alerts for all FDA-regulated products is [<http://www.fda.gov/opacom/7alerts.html>].

Comparison of Device and Drug Models for Regulation

The regulatory system for drugs was created in order to reduce medical “quackery” in the early 1900s. The first FFDC Act required drugmakers to prove to FDA that their product worked for the use they were promoting, and required agency approval for testing, production and marketing. At that time, few medical devices existed. As a result of rapid advances in medical technology in the 1960s, the device amendments were added more recently in the history of medical product regulation,

and were designed to facilitate rapid innovation that is characteristic of the industry.⁴³ Because of differences in the evolution of statutory authority over drugs and devices reflecting differences in the respective industries and products, different regulatory review processes emerged. Functional review of drugs and devices is organizationally separated within different centers of FDA (with coordination of review for combination products, such as a drug-delivering device).

Industry and Product Related Factors

The medical device industry on a whole is much smaller than the pharmaceutical industry, with estimated earnings of \$80 billion in 2004 compared to the drug industry's estimated \$222 billion (see **Table 2**).⁴⁴ As a result, device companies often do not have the economic or financial resources of multi-billion dollar drug companies. Furthermore, the medical device market is highly fragmented: surgical and medical supplies make up the largest sector, followed by IVDs, cardiovascular devices, orthopedic devices, and diagnostic imaging.⁴⁵ Although the largest companies dominate the market for devices in terms of sales, it is often the small companies that make a significant contribution to early innovation. They later will often partner with larger companies to bring products to market, because small companies often lack access to capital, and often lack resources to conduct clinical trials and navigate the regulatory and reimbursement hurdles.

Devices are usually intended to treat fewer patients than drugs, and they are often used for only a few years before being replaced with newer models or therapies. Typically, there is initially a truly innovative device, which is then incrementally modified several to many times over the course of its relatively short product life. Given the dynamic process of improvement, regulatory requirements for incremental modifications to approved devices are generally much less stringent than modifications to approved drugs and/or their manufacturing process.

There are more incentives to encourage drug manufacturers to develop new drugs built into the regulatory framework. The Orphan Drug Act (P.L. 97-414) guarantees the developer of an orphan product seven years of market exclusivity following the approval of the product by the FDA. During a time of market

⁴³ R A. Merrill, "Regulation of Drugs and Devices: An Evolution," *Health Affairs*, vol. 13, no. 3 (1994): pp. 47-70.

⁴⁴ U.S. Department of Commerce, International Trade Commission verbal estimates given to Michele Schoonmaker, Jan. 2005. The \$80 billion for devices includes both medical devices and medical supplies. The \$222 billion for drugs was based on the Department of Commerce's estimate of a \$500 billion global market for drugs, of which they estimate that the U.S. market is approximately 44% (same proportion as for devices). It was unclear if the estimate for drugs included over-the-counter drugs that are available without a prescription. See also CRS Report RL3134, *Health Expenditures in 2002*. In this report, it is estimated that \$162.4 billion was spent in 2002 for prescription drugs in the United States. Estimates for expenditures on over-the-counter drugs range from \$5 to \$19 billion.

⁴⁵ The Legin Group, for AdvaMed, *The Impact of Regulation and Market Dynamics on Innovation: The State of the Industry* (Washington, D.C., 2001).

exclusivity, FDA will not approve other competitive products for the same use. Market exclusivity was also authorized by FDAMA wherein a drug manufacturer could gain an additional six months exclusivity for performing studies in a pediatric population at the agency's request. Market exclusivity does not apply for devices. Instead, under MDUFMA, device manufacturers can have application fees waived for performing studies that the FDA requests (e.g., pediatric studies).

Market exclusivity does not extend a drug manufacturer's patent (although FDA will not approve a generic drug during a period of market exclusivity). Extensions of patent beyond the 20 years presently granted are available for drugs and devices with an NDA or PMA approved by FDA. These extensions are granted by the Patent and Trademark Office (PTO), in consultation with FDA. The length of the extension is variable, but it can be up to half of the time it takes to do a clinical trial. For drugs, the clock starts when the Investigational New Drug (IND) application is approved (i.e., before the clinical trial starts). For devices, the clock starts when the clinical trial starts. Historically, the average patent extension has been greater for drugs because of where the clock started, and because drug trials took longer to complete than device trials.

FDA Review and Approval Processes

A greater number of drugs typically undergo more intense review compared to devices, because there is no risk-based classification for them. Fewer devices, in contrast, receive intense review. Most devices are cleared on substantial equivalence based on comparative performance characteristics rather than actual clinical data.

Premarket. The premarket review phase for a drug is significantly longer compared to that for a device. Both drugs and devices have a special regulatory category for "investigational use" that allows for shipment of an unapproved product for clinical research purposes. Clinical trials for drugs cannot begin without an (IND) application filed with FDA. These are approved (or not) based on the preclinical data provided. In contrast, IDEs are mainly required for a smaller group of devices, usually those that are invasive, life-sustaining or high risk. Preclinical testing for drugs is far more extensive than that for most devices (with the exception being new implantable or life-sustaining devices, which may require animal studies). Drug studies include computer modeling, animal testing, in vitro (i.e., test tube) studies, and human studies, including toxicology studies, such as investigations into how the drug is metabolized, where the drug and metabolites are distributed in the body, how fast the drug and metabolites are cleared from the body. Preclinical data is almost never required for Class I and II devices, or IVDs.

For both drugs and devices, valid scientific evidence is required to meet a threshold for "safety" and "effectiveness."⁴⁶ FDAMA modified FFDC Act requirements from two to one adequate and well-controlled study, and also permitted use of surrogate endpoints for approval rather than clinical endpoints. The majority

⁴⁶ FDA, *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, May, 1998, at [<http://www.fda.gov/cder/guidance/1397fnl.pdf>].

of devices, especially diagnostic devices (all classes) and other devices that are cleared under substantial equivalence, do not undergo “clinical trials” in the sense that patients are not broken into two groups: one receiving the product (intervention) and the other receiving an alternative. Studies for most devices are comparative performance on the same samples or in a similar set of circumstances. Neither similar drugs nor similar devices are routinely directly compared in order to assess relative effectiveness of one product over another.

Drugs do not have a true “substantial equivalence” standard. Even generic drugs, which are compounds similar to brand name pharmaceuticals in dosage, safety, strength, route of administration, quality, performance and intended use, undergo a similar review and approval process as the original. The application for a generic drug is called an abbreviated new drug application (ANDA).⁴⁷ The standard for approval is “bioequivalence” which means that the manufacturer needs to demonstrate that generic delivers the same amount of active ingredient to the blood stream of healthy volunteers in the same amount of time as the original. All drug manufacturers must undergo inspection (where device manufacturers can, but often are not inspected), and must adhere to GMP and labeling regulations. The target review time for an ANDA is 180 days although unlike a 510(k) for devices, the review time for an ANDA is actually longer than the more stringent NDA.

User fees (i.e., fees paid to FDA by manufacturers applying for market approval) for drugs are significantly higher than those for devices.

Postmarket. It has proved extremely difficult for FDA to remove a product from the market once it has been cleared or approved. Questionable performance in the premarket phase may generate restrictive labeling or indications and may trigger a requirement for the manufacturer to conduct a postmarket study. Postmarket studies are more common for drugs than devices. Alternatively, certain high-risk medical devices can be subject to medical device tracking requirements. Devices are more conducive to tracking requirements than are drugs because patient compliance can often be verified (e.g., the patient has the device or does not, whereas it is sometimes difficult to tell whether patients are compliant in taking their medication), and because fewer devices need to be followed. FDA posts all recalls, market withdrawals and safety alerts on its main website for all of its regulated products.⁴⁸

⁴⁷ FDA, *Abbreviated New Drug Application Process for Generic Drugs*, Dec. 30, 2003, at [<http://www.fda.gov/cder/regulatory/applications/anda.htm>].

⁴⁸ [<http://www.fda.gov/opacom/7alerts.html>].

Table 2. Comparison of the Drug and Device Approval Processes

Industry Variables	Drugs (CDER data)	Medical Devices (CDRH data)
U.S. Market size (2004)	\$222 billion	\$80 billion (includes medical supplies)
Average product lifetime	decades	years
Special incentives for development	Market exclusivity after approval (determined by FDA), patent extension for regulatory process (determined by Patent office), pediatric exclusivity, orphan drug process for rare diseases, waived fees for certain types of submissions (agency defined).	Patent extension for regulatory process (determined by Patent office) Humanitarian device exemption for rare diseases, no pediatric exclusivity, but waived fees for certain types of submissions (such as pediatric studies, agency defined).
FDA Variables		
Premarket review	Required for all drugs	Some devices exempt
Type of submission and 2005 user fees	Not dependent on risk to patient — NDA (new drug application), — ANDA (abbreviated new drug application) for generic drugs. User fees: — \$672,000 for an application requiring clinical data, — \$336,000 for an application not requiring clinical data or a supplement requiring clinical data — \$262,200 (establishment fees) — \$41,710 (product fees)	Dependent on risk-based classification; — PMA for high risk devices (\$239,237, standard; \$90,910 for small business). — 510(k) for low/moderate risk devices (\$3,502 standard; \$2,802 for small business).

FDA Variables		
Premarket review	Drugs	Medical devices
Total number of submissions, all types, in 2003	2,104 received, 2,019 decisions made (a)	9,872 received; 9,570 completed; 4,740 decisions made (b)
Total number of submissions, all types, Approved/cleared in 2003	1,641 (2,019)	4,292 (4,740)
Total number of submissions, all types, Approvable, in 2003	249 (2,019)	115 (4,740)
Total number of submissions, all types, Not approvable in 2003	79 (2,019)	63 (4,740)
Total number of submissions, all types, Withdrawn (drugs) Not approved (devices) in 2003	50 (2,019)	270 (4,740)
Standard for approval	NDA, Efficacy supplements: safety and effectiveness ANDA: bioequivalence	PMA, de novo 510(k): safety and effectiveness other 510(k): substantial equivalence.

FDA Variables		
Premarket review	Drugs	Medical Devices
Types of studies	<p><i>Safety and effectiveness:</i> preclinical and interventional clinical trials often done; data from at least one controlled clinical trial may suffice; approval can be granted based on a surrogate endpoint (21 CFR § 314.510), however, approval under this section is subject to postmarket studies to verify clinical benefit</p> <p><i>Bioequivalence:</i> requires demonstration that the generic form of an original drug, used at the same dose intended for the same population, delivers active ingredient in the same amount at the same rate.</p> <p>Summaries of approved applications available on website.</p>	<p><i>Safety and effectiveness:</i> preclinical and interventional clinical trials done for implantable or life-sustaining devices may investigate clinical outcome), if a ‘next generation’ studies endpoints are a surrogate marker of disease or health; interventional trial rarely done for diagnostic devices; <i>Substantial equivalence:</i> comparison of device performance to another legally marketed device using clinical or analytical samples.</p> <p>Summaries of approved/cleared applications available on website</p>
FDA Average Review time (days), 2003	NDA: 231 (priority, i.e., significant improvement), 357 (standard) ANDA: 510	PMA: 151 510(k): 76
Postmarket surveillance	MedWatch: searchable webpage for medical product safety information	MedWatch: searchable webpage for medical product safety information
Adverse Event Reporting (time indicates days after becoming aware of an incident)	<p>Manufacturers report to FDA:</p> <ul style="list-style-type: none"> — Serious and unexpected events within 15 calendar days — Individual reports available on website, but difficult to search 	<p>Manufacturers report to FDA:</p> <ul style="list-style-type: none"> — Deaths, serious injuries, malfunctions within 30 calendar days — Serious events requiring remedial action: 5 working days <p>User facilities report to FDA:</p> <ul style="list-style-type: none"> — Death & serious injury: within 10 working days <p>Individual reports available on website (Medical Device Reporting database)</p>

Postmarket surveillance	Drugs	Medical Devices
Number of reports received, 2003	370,887: — 22,955 MedWatch reports directly from individuals — 144,310 manufacturer 15-day (expedited) reports — 58,998 serious manufacturer periodic reports — 144,624 nonserious manufacturer periodic reports	64,369: — 60,767 individual medical device adverse event reports from manufacturers, user facilities, and importers, and — 3,602 voluntary reports from health care professionals and the public
Tracking	Not required	Required for implantable, life-sustaining or other high risk devices as defined
Number safety-based market withdrawals in 2003	0	5

Sources: Center for Devices and Radiological Health (CDRH): Office of Device Evaluation/Office of In Vitro Diagnostic Device Evaluation and Safety (ODE/OIVD), *Annual Report: Fiscal Year 2003*, at [<http://www.fda.gov/cdrh/annual/fy2003/ode/>]. And CDRH, *FY2003 CDRH Annual Report*, at [<http://www.fda.gov/cdrh/annual/fy2003/assuring.html#postmarket>]. Center for Drug Evaluation and Research (CDER), *CDER New Drug and Biologic Approval Reports: 2003*, (drug only), at [<http://www.fda.gov/cder/rdmt/default.htm>], and CDER, “*CDER Report to the Nation: 2003*,” at [<http://www.fda.gov/cder/reports/rtn/2003/rtn2003-3.HTM#AERS>].

Notes: U.S. market size data were supplied by the Department of Commerce (see footnote 44). Other numerical data are for CDER (drugs) and CDRH (devices) only; the percentage of devices regulated by the Center for Biologics Evaluation and Research (CBER) is small compared to CDRH. At the time of writing this report, exact numbers of devices reviewed by CBER were unavailable for 2003. (a) The numbers reflect submissions for NDAs, resubmitted NDAs, manufacturing supplements, efficacy supplements (new uses for approved drugs), and resubmitted efficacy supplements. Applications which are “withdrawn” or “not approvable” may be resubmitted with new data at any time. (b) The number of decisions made includes data for: Premarket Applications (PMAs), PMA Supplements, Humanitarian Device Exemptions (HDEs), HDE Supplements, Investigational Device Exemptions (IDEs), IDE Amendments, and 510(k)s. Data do not include 4,424 decisions made for IDE Supplements, because the breakdown of data by decision status was not available. An additional 648 applications were either withdrawn from FDA consideration by the manufacturer or had another administrative action imposed that did not result in a decision. Data for approvable/not approvable were not available for IDEs, IDE Amendments and 510(k) because that is not a relevant decision for those types of submissions.