Chapter 3
Medical Device Development

The medical device industry in the United States and worldwide is immense in its economic impact (sales in 2009 were $260 billion worldwide, $120 billion in the United States alone, $64 billion in the European Community, and $45 billion in Japan; in 1998 the US medical equipment trade surplus was $18.2 billion). Between 87,000 and 140,000 different devices are produced in the United States annually by approximately 8,200 different manufacturers employing some 311,000 people. Furthermore, it is believed that more than 1,000 of these manufacturers are development-stage only companies without products yet on the market. Medical devices are or extreme importance to the health of the citizens of the world (Nugent 1994; The Wilkerson Group 1999) (see Table 3.1). While it is true that the large companies dominate the market in terms of sales and revenue, just as with pharmaceuticals it is the small companies that dominate innovation. The assessment of the safety to patients using the multitude of items produced by this industry is dependent on schemes and methods that are largely peculiar to these kinds of products, are not as rigorous as those employed for foods, drugs, and pesticides, and are in a persistent state of flux. Regulation of such devices is, in fact, relatively new. It is only with the Medical Device Amendments (to the Food, Drug and Cosmetic Act of 1976) that devices have come to be explicitly regulated at all, and with the Safe Medical Devices Act of 1990, the Medical Device Amendments Act of 1992, and subsequent laws that the regulation of devices for biocompatibility became rigorous (see Table 3.2). According to section 201(h) of the Food, Drug and Cosmetic Act, a medical device is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component, part, or accessory that is:

> Recognized in the official National Formulary, or the United States Pharmacopeia (USP 2000), or any supplement to them.
>
> Intended for use in the diagnosis of disease, in man or other animals.
>
> Intended to affect the structure or any function of the body of man or other animals, and that does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals, and that is not dependent upon being metabolized for the achievement of any of its principal intended purposes (CDRH 1992).

S.C. Gad and C.B. Spainhour, *Contract Research and Development Organizations: Their Role in Global Product Development*, DOI 10.1007/978-1-4614-0049-3_3,
© Springer Science+Business Media, LLC 2011

Table 3.1 The largest US medical device markets (2001)

US medical device markets (2001) (US $ in billions)	
Diagnostics (in vitro)	20.5
Surgery (min. invasive)	16.4
Orthopedic	14.7
Wound care	13.0
Cardiovascular	12.5

Table 3.2 FDA classification of preamendment medical devices

Part number	Title	Date of publication
21 CFR Part 862	Clinical chemistry and clinical toxicology	May 1, 1987
21 CFR Part 864	Hematology and pathology devices	May 11, 1987
21 CFR Part 866	Immunology and microbiology	November 9, 1982
21 CFR Part 868	Anesthesiology devices	July 16, 1982
21 CFR Part 870	Cardiovascular devices	February 5, 1980
21 CFR Part 872	Dental devices	August 12, 1987
21 CFR Part 874	Ear, nose, and throat devices	November 6, 1986
21 CFR Part 876	Gastroenterology–urology devices	November 23, 1983
21 CFR Part 878	General and plastic surgery devices	June 24, 1988
21 CFR Part 880	General hospital and personal use	October 21, 1980
21 CFR Part 882	Neurological devices	November 4, 1979
21 CFR Part 884	Obstetrical and gynecological devices	February 26, 1980
21 CFR Part 886	Ophthalmic devices	September 2, 1987
21 CFR Part 888	Orthopedic devices	September 4, 1987
21 CFR Part 890	Physical medicine devices	November 23, 1983
21 CFR Part 892	Radiological devices	January 20, 1988

- FDA determines that the device is substantially equivalent to another device that was not in commercial distribution before such date but that has since been classified into class I or II (through the 510(k) process).
- FDA reclassifies the device into Class I or II.

The procedures for reclassifying a "postamendment" class III device are codified in 21 CFR section 860.134(b) (1)–(7).

The device classification process continues to this day. As FDA becomes aware of new devices that require formal classification or pre-1976 devices that were somehow overlooked in the original classification procedures, the agency initiates new classification proceedings, again requesting the recommendation of one or more of the appropriate advisory panels.

Under this definition, devices might be considered as belonging to one of nine categories (North American industrial classification): surgical and medical instruments, ophthalmic, dental, laboratory apparatus, irradiation, specialty devices, medical/surgical supplies, in vitro diagnostics, and electromedical. There were (in 2000) 16,170 companies involved in these sectors – 6,750 of them manufacturers worldwide.

Table 3.3 The ten projected biggest growth device products (in 2000)

Rank	Product	Percentage revenue growth rate (years)	Specialty
1	Fibrin sealants	174.6 (1995–2002)	Wound care
2	Solid artificial organs	141.2 (1995–2002)	Transplant/implant
3	Left ventricular assist devices	96.0 (1995–2002)	Cardiovascular
4	Skin substitute products	63.1 (1997–2004)	Wound care
5	Refractive surgical devices	54.4 (1998–2005)	Ophthalmic
6	Gynecologic fallopscopes	49.5 (1995–2000)	Endoscopic/MIS
7	PTMR products	47.8 (2000–2004)	Cardiovascular
8	Bone growth substitutes and growth factors	47.0 (1997–2004)	Orthopedics
9	Growth factor dressings	46.0 (1997–2004)	Wound care
10	Vascular stent-grafts	46.0 (1997–2004)	Cardiovascular

This is a global industry with a $260 billion annual market. The US market alone is $120 billion, or 42% of this (MDDI 2000) (see Table 3.3).

The top 20 medical devices in terms of revenues in 1999 were the following:

1. Incontinence supplies
2. Home blood glucose-monitoring products
3. Wound closure products
4. Implantable defibrillators
5. Soft contact lenses
6. Orthopedic fixation devices
7. Pacemakers
8. Examination gloves
9. Interventional cardiovascular coronary stents
10. Arthroscopic accessory instruments
11. Prosthetic knee joint implants
12. Lens care products
13. Prosthetic hip joint implants
14. Multiparameter patient-monitoring equipment
15. Mechanical wound closure
16. Wound suture products
17. Absorbable polymers
18. Hearing aids
19. Wheelchair and scooter/mobility aids
20. Peritoneal dialysis sets (The Wilkerson Group 1999)

The steps and processes involved in developing and bringing to market a new medical device are significantly different than those in pharmaceutical development (Gad 2010). This process, while less complex, less expensive, and shorter than that for a drug, is also less well defined and less profitable if successful. But the fundamental objectives in development and approval are the same as for a drug – to have a product that can be profitably marketed with proven therapeutic efficacy and safety.

There are two significant routes to regulatory approval (and therefore development) for a device (Kahan 2000), 510(k) and PMA (premarket approval). The 510(k) route is less rigorous but requires that the device be either Class I or II (the lower two categories of risks) and that there already be a similar ("predicate") device on the market. Such devices may or may not require clinical studies (efficacy and safety may be adequately established in nonclinical studies). Suitable materials must be utilized (and analytical data must be available to establish that the levels of purity and nature of impurities in said materials are acceptable), and the resulting actual product must be sterilized, packaged, and labeled in accordance with regulatory requirements. Also a 510(k) application must be assembled, submitted, and approved by CDRH (Center for Devices and Radiological Health). Such applications account for roughly 98% of new devices, with only 10% of such applications requiring some sort of clinical testing (*Note*: There is a 510(j) route of approval, but it is very rare and will not be discussed here).

The other route for approval requires a PMA. Devices coming to market by this regulatory route include all of those in Class III and also those in Class II that either do not have a predicate or are of some specified category. Clinical studies must always be performed for these to both demonstrate efficacy and evaluate safety in clinical use.

Biocompatibility

The year 1990 saw the passage of the Safe Medical Devices Act, which made premarketing requirements and postmarketing surveillance more rigorous. The actual current guidelines for testing originated with the USP guidance on the biocompatibility of plastics. A formal regulatory approach springs from the Tripartite Agreement, which is a joint intergovernmental agreement between the United Kingdom, Canada, and the United States (with France having joined later). After lengthy consideration, the FDA announced acceptance of International Standards Organization (ISO) 1993 guidelines for testing (ASTM 1990; FAO 1991; MAPI 1992; O'Grady 1990; Spizizen 1992) under the rubric of harmonization. This is the second major trend operative in device regulation: the internationalization of the marketplace with accompanying efforts to harmonize regulations. Under the efforts of the ICH (International Conference on Harmonization), great strides have been made in this area.

Independent of FDA initiatives, the USP has promulgated test methods and standards for various aspects of establishing the safety of drugs (e.g., the recent standards for inclusion of the levels of volatiles in formulated drug products), which were, in effect, regulations affecting the safety of both drugs and devices. Most of the actual current guidelines for the conduct of nonclinical safety evaluations of medical devices have evolved from such quasi-agency actions [e.g., the USP's 1965 promulgation of biological tests for plastics and ongoing American National Standards Institute's (ANSI) standard promulgation].

A medical device that is adequately designed for its intended use should be safe for that use. The device should not release any harmful substances into the patient that can subsequently lead to any adverse biologic effects. Some manufacturers believe that biocompatibility is sufficiently indicated if their devices are made of

medical grade material or materials approved by FDA as direct or indirect additives. The term medical grade does not have an accepted legal or regulatory definition and therefore can be misleading without appropriate biocompatibility testing.

There are no universally accepted definitions for biomaterial and biocompatibility, yet the manufacturer who ultimately markets a device will be required by the Parenteral Drug Association (PDA) to demonstrate biocompatibility of the product as part of the assurance of its safety and effectiveness. The manufacturer is responsible for understanding biocompatibility tests and selecting methods that best demonstrate the following:

- The lack of adverse biological response from the biomaterial.
- The absence of adverse effects on patients.

The diversity of the materials used, types of medical devices, intended uses, exposures, and potential harms present an enormous challenge to the design and conduct of well-designed biocompatibility testing programs. The experience gained in one application area is not necessarily transferable to another application. The same applies to different or sometimes slightly different (variable) materials. Biodegradation and interaction of materials complicate and confound the assessment.

Biocompatibility describes the state of a biomaterial within a physiological environment without the material adversely affecting the tissue or the tissue adversely affecting the material. Biocompatibility is both a chemical and physical interaction between the material and the tissue and the biological response to these reactions.

Biocompatibility assays are used to predict and prevent adverse reactions and establish the absence of any harmful effects of the material. Such assays help to determine the potential risk that the material may pose to the patient. The proper use of biocompatibility tests can reject potentially harmful materials while permitting safe materials to be used for manufacturing the device.

Any biocompatibility statement is useful only when it is considered in the proper context. A statement such as “propylene is biocompatible” lacks precision and can lead to misunderstanding. Any statement of biocompatibility should include information on the type of device, the intended conditions of use, the degree of patient contact, and the potential of the device to cause harm. Manufacturers should avoid using the term “biocompatible” without clearly identifying the environment in which it is used and any limitations on such use.

The need for biocompatibility testing and the extent of such testing that should be performed depends on numerous factors. These factors include the type of device, intended use, liability, degree of patient contact, nature of the components, and potential of the device to cause harm. There are no universal tests to satisfy all situations, and there is no single test that can predict biological performance of the material or device and reliably predict the safety of the device. The types and intended uses of medical devices determine the types and number of tests required to establish biocompatibility. Biological tests should be performed under conditions that stimulate the actual use of the product or material as closely as possible and should demonstrate the biocompatibility of a material or device for the specifically intended use. These tests will be more extensive for a new material than for those materials that have an established history of long and safe uses.

All materials used in the manufacture of a medical device should be considered for an evaluation of their suitability for intended use. Consideration should always be given to the possibility of the release of toxic substances from the base material(s), as well as any contaminants that might remain after the manufacturing process or sterilization. The extent of these investigations will vary, depending on previously known information (prior art) and initial screening tests.

Fundamentals of Biocompatibility Tests

Biocompatibility is generally demonstrated by tests utilizing toxicological principles that provide information on the potential toxicity of materials in the clinical application (Gad 2002). Many classical toxicological tests, however, were developed for a pure chemical agent, and are not applicable to biocompatibility testing of materials. In addition, medical devices are an unusual test subject in toxicity testing. A biomaterial is a complex entity of multiple components, and the material toxicity is mediated by both its physical and chemical properties. The toxicity from a given biomaterial often comes from its leachable components, and the chemical composition of a material is often not known or not known with precision. Toxicological information on the material and its chemical composition is seldom available, and the possible interactions among the components in any given biological test system are seldom known.

Accordingly, biocompatibility should not be defined by a single test. It is highly unlikely that a single parameter will be able to ensure biocompatibility; therefore, it is necessary to test as many biocompatibility parameters as appropriate. It is also important to test as many samples as possible, therefore suitable positive and negative controls should produce a standard response index for repeated tests.

Additionally, the use of exaggerated conditions, such as using higher dose ranges and longer contact durations or multiple insults that are more severe by many factors than the actual condition(s) of use, is important. Adopting an acceptable clinical exposure level that is multiple factors below the lowest toxic level has been a general practice.

Most of the biocompatibility tests are short-term tests designed to establish acute toxicity. Data from these short-term tests should not be extrapolated to cover the areas with longer periods of exposure in which no test results are available.

Biocompatibility testing should be designed to assess the potential adverse effects under actual use conditions or specific conditions close to the actual use conditions. The physical and biological data obtained from biocompatibility tests should be correlated to the device and its use. Accuracy, reproducibility, and interpretability of tests depend on the method and the equipment used and the investigator's skill and experience.

There are several toxicological principles that the investigator must consider before planning biocompatibility testing programs. Biocompatibility depends on the tissue or tissues that contact the device. For example, the requirements for a blood-contacting device would be different from those applicable to a urethral catheter.

Also, the degree of biocompatibility assurance depends on the involvement and the duration of contact with the human body. Some materials, such as those used in orthopedic implants, are meant to last for a long period of time in the patient. In this case, a biocompatibility testing program needs to show that the implant does not adversely affect the body during the long period of use. The possibility of biodegradation of material or device should not be ignored. Biodegradation by the body can change an implant's safety and effectiveness. The leachables from plastic used during a hemodialysis procedure may be very low, but the patient who is dialyzed 3 times a week may be exposed to a total of several grams during his or her lifetime, therefore the cumulative effects (chronic exposure) should be assessed.

Two materials having the same chemical composition but different physical characteristics may not induce the same biological response. Also, past biological experiences with seemingly identical materials have their limits, too. Toxicity may come from leachable components of the material due to differences in formulation and manufacturing procedures.

Empirical correlation between biocompatibility testing results and actual toxic findings in humans and the extrapolation of the quantitative results from short-term in vitro testing to quantitative toxicity at the time of use are controversial. Such accumulation of data needs a thorough, cautious, careful, and scientifically sound interpretation and explanation within the boundaries of the information at hand. The control of variation in the assessment of biological susceptibility and resistance to obtain a biological response range for a toxic effect needs careful attention as does an assessment of the host factors that determine the variability of susceptibility in a toxicological response adjustment to susceptibility. The variability in human populations also needs careful attention.

The challenge of the assessment of biocompatibility is to create and use knowledge to reduce the degree of unknowns in the development process and in turn use this information to help make the best possible decisions pertaining to actual conditions of use. The hazard presented by a substance, with its inherent toxic potential, can only be manifested when fully exposed in a patient. Risk, which is actual or potential harm, is therefore a function of toxic hazard and exposure. The safety of any leachables contained in the device or on the surface can be evaluated by determining the total amount of potentially harmful substance, estimating the amount reaching the patient's tissues, assessing the risk of exposure, and then performing a risk vs. benefit analysis. Then the potential harm from the use of biomaterial is completely identified from the biocompatibility analyses and data of an alternate material.

Clinical Testing

Current data indicate that large medical device developers are conducting fewer studies at fewer locations, but the sheer number of products in the pipeline is providing significant opportunities for investigative sites and CROs with experience conducting

Table 3.4 Clinical grant spending for medical device trials in the United States

1994	$100
1998	$250
2002	$530

Table 3.5 Original investigational device exemptions (IDEs) approved

Number of IDEs	
1991	220
1993	248
1995	210
1997	272
1999	305
2001	284
2002	307
2003	246
2004	217
2005	238
2006	234
2007	214
2008	215

device trials. Indeed, spending on clinical medical device studies remains one of the fastest growing segments (see Table 3.4).

Whereas spending for clinical studies of drug therapies grew 14% annually over the past several years, spending for devices grew by more than 20% annually in that same period. It is estimated that sponsors will spend more than half a billion dollars on clinical research for medical device trials in 2002. Sponsor's use of CROs to manage device trials is also growing substantially. The driver of growth in medical device trials is not regulatory pressure, as is often the case. It is the medical community. "Doctors are clearly the ones driving most of the research," said Charlie Whelan, an industry analyst in the medical device group of San Jose, CA based Frost and Sullivan. "They're conservative by nature and won't use something until they feel there's sufficient clinical evidence to support its use. Some doctors want more data than the FDA requires. They want longer-term data or want answers to more specific questions."

The persistent pattern of filings in this market is expected to continue and possibly grow with enhanced physician demand for clinical trial evidence and a rich pipeline of potential new devices (Table 3.5).

Although the number of original investigational device exemption (IDE) applications dropped slightly between 2000 and 2001, the numbers of PMAs and PMA supplements have been increasing steadily. These devices are novel and present

potentially higher risk. They also require more pre- and postmarketing clinical research studies. “There is no shortage of opportunity in this market segment,” said Whelan. “Many hundreds of new device companies have been created in each of the past five years, fueled by an aging population and new technologies.”

Market Characteristics

The global medical device market, excluding imaging and clinical diagnostics, is valued at over $150 billion annually. Product lines are numerous and diverse, ranging from latex gloves and wheelchairs to hearing aids and artificial hearts. About 80% of the medical device market is composed of small companies with fewer than 50 employees. Nearly one-fourth of the 13,000-plus medical device and diagnostics manufacturers are startup companies with no source of revenue. This fragmentation mirrors the multitude of small markets for a widely diverse range of devices used in medical interventions.

The strategy for most manufacturers is to get a 510(k), then do a clinical study. It is not an “investigation device” anymore, and the FDA never sees the data. The studies are still subject to Part 56 and Part 50 regulations regarding IRB approval and informed consent, but the FDA has no tools or means to effectively monitor and insure compliance.

Europe is again seeing a healthy portion of the activity, largely because devices are far less regulated across the Atlantic than in the United States. The only ethical regulatory strategy that makes sense is to first do a clinical study in Europe and get approval and then come to the United States. Most often clinical trials are conducted in Europe where they tend to be larger projects with an average of 531 subjects per study vs. 172 on average in the United States. Companies specifically conduct five clinical studies to bring a device to market in Europe, more than twice the US average. Unlike the increasingly global nature of clinical trials for ethical pharmaceuticals, medical device trials are becoming less international.

Device companies are placing their studies in many of the same places where drug studies are conducted. Typically, clinical studies go to leading academic institutions where the prevalence of disease in the patient population is most representative.

According to Frost and Sullivan, medical device companies contract out less than 5% of their clinical research projects to CROs (see Table 3.6). “They use CROs a lot less than drug companies,” said Whelan. “Our forecast suggests that, in coming years, the medical device industry is likely to outsource more of its R&D, but not very much – i.e., up to maybe 7% by 2005.” Most of the research that needs to be done can typically be done in-house. Doing research through a CRO also exposes the company to a lot of risk, including patent infringement. There are an estimated half dozen CROs in the United States and another half dozen in Europe that cater mostly, if not exclusively, to medical device companies. Many of them are boutique CROs that specialize in particular types of devices. All of them are fairly small, with

Table 3.6 Increasing use of CROs for medical device trials

Percentage of device companies who report using CRO for the years 1998 and 2001

	1998 (%)	2001 (%)
Protocol design	0	11
CRF design	0	12
Monitoring services	13	29
Regulatory services	8	11
Statistical services	8	33

between 5 and 30 employees. The big, multipurpose CROs, like Quintiles and Parexel, also assist sponsors with device trials. About 96% of medical device manufacturers utilize CROs most frequently for statistical and monitoring services.

Changing Focus, Changing Oversight

The US device industry is continuously developing new and innovative techniques in areas such as molecular diagnostics (including test for infectious diseases, inherited and metabolic diseases, and cancer), minimally invasive surgery, biocompatible materials used for cardiovascular purposes, and orthopedic implants.

Combination products, gene therapies, and imaging technologies and devices that can be linked to bioterrorism are among the hottest areas of medical device research currently.

A recent report by Frost and Sullivan named digital radiography and molecular diagnostics as two sectors worth watching for new developments in the months ahead. As healthcare providers shift to digital radiography techniques, image integration will gain in importance. Financial simulation will gain in importance. The simultaneous shift toward home health care and nursing home care is also bound to spur demand – and thus the launch of even more new products – ranging from ambulatory aids to orthopedic supports. "Products focusing on self-care, the geriatric population and women are likely to experience impressive growth," a recent report has stated.

Regulations are as stringent for devices as for drugs, claim FDA officials (see Table 3.7). Submission-to-decision review times, however, are now worse for original PMAs than for New Drug Applications – 411 vs. 365 days – and the highest since the passage of FDAMA. Review times on 501(k)s, meanwhile, are falling. Third-party review of eligible Class I and II 510(k) devices, paid for by the manufacturer, is very small – but growing – contributor to review spending. The CDRH's Office of Device Evaluation (ODE) received only 107 510(k)s reviewed by third-party organizations in FY 2001, which amounted to about 16% of all eligible 510(k). However, that is a 128% increase over the 47 such submissions received the prior year. Expansion of the pilot program in March 2001 more than tripled the number of eligible devices to 670.

Table 3.7 Improving development performance

Percentage of IDEs approved by FDA in first review cycle	
1997	69%
1999	68%
2001	80%

As the FDA itself reports, the frequency and consequence of hazards resulting from medical use error far exceed those arising from device failures. So the FDA is paying far more attention to device design and labeling. The Office of Health and Industry Programs (OHIP) assists CDRH's ODE by providing "human factors reviews" for PMA and 510(k) devices. This included patient labeling reviews on 141 submissions to CDRH last year. The OHIP also issued a guidance document last year on medical device patient labeling, including a suggested sequence and content, and principles on the appearance of text and graphics.

Guidance has also been issued about when a device manufacturer may report changes or modifications to the clinical protocol in a 5-day notice to the IRB as opposed to getting formal FDA approval. It clarifies the kind of protocol changes – i.e., modification of inclusion/exclusion criteria to better define the target patient population or increasing the frequency at which data are gathered – appropriate for the 5-day notice provision. Other types of changes, such as the indication or type of study control, require prior approval.

The FDA has also posted for comment a proposed regulatory change that would require sponsors and investigators to disclose to an IRB any prior IRB review of a proposed study. In the device world companies do IRB shopping since the IRB makes the determination if the device poses significant (SR) or nonsignificant risk (NSR).

Device manufacturers share with pharmaceutical companies the headache of complying with the Health Insurance Portability and Accountability Act (HIPAA). In terms of sponsor access to source data, there must be statement of when authorization expires, such as until the PMA is approved or when the product is on the market. There should be a description of how far back in time the patient's medical records will need to be searched. The consent process should also include a statement that treatment, payment, and insurance reimbursement are not conditioned on signing. The document should specifically indicate information that will not be disclosed to the sponsor. And there should be a statement of when, and if, study data will be made available to study subjects. Even though the sponsor pays for a lab test, it becomes part of the patient's medical record. Patients have a right to see it unless they sign away that right during the consent process.

Under HIPAA, doctors will no longer have the right to look at the medical records of referred patients, even those within the same practice group. Investigators will need to go to the IRB to ask for a "waiver of authorization." That will add another 2–3 months to the timeline. The IRB must also get educated.

The Review Speed Problem

Device manufacturers have been pressuring the FDA to accelerate the review and approval cycle time. The average useful life span of a medical device is 18 months. It is not a question of the patent expiring. Within 18 months, the product maybe obsolete. A competitor has a new bell or whistle that makes their product more desirable than yours.

In terms of review speed, FDAMA has clearly done more to benefit pharmaceutical companies than device firms. With breakthrough technology, the FDA has "a tendency to request information for 'educational purposes' that is not directly pertinent to determine the safety and effectiveness of the device in question," Weagraff explained. Timeliness and responsiveness could be improved.

A central problem at the FDA is a lack of resources and appropriately trained resources to review the mandatory, more complicated studies. "A growing number of premarket submissions are for medical technologies that pose novel review issues, like tissue-engineered products, hybrid technologies…and nanotechnology," according to the industry trade group AdvaMed.

Last year, the FDA received 70 PMA applications, the highest number in 10 years. The CDRH alone reviews some 17,000 device submissions and inspects 15,000 manufacturers a year. Though a proposed $10 million budget increase for the agency was awarded in 2003, none of these funds were earmarked for device review. "The FDA device program budget has remained essentially flat over the last 10 years, and has declined in real dollars after accounting for inflation," according to the AdvaMed report. "In addition, staffing levels have declined 8% since 1995." Limited resources have also prevented the FDA from offering up more device-specific guidance documents.

The FDA claims to be focusing on erasing holdups on PMA combination product reviews that often involve the expertise of "a drug person, a materials person and an engineer," according to one CDRH official. "The experts are all in-house, they're just not all in our center. And what's a priority for us is not necessarily a priority for anyone else." In the past, the FDA has taken as long as 13 months simply to decide which agency – CDRH, the Center for Drug Evaluation and Research, or the Center for Biologics Evaluation and Research – should perform the review. In February, the FDA also established a combination products program to help deal with the delays. Legislation is pending to create a formal combination products office to assign products to the appropriate component of the FDA.

Mark Kramer, director of the program housed in the FDA's Office of the Ombudsman, said, "Currently, we don't have an exact count on the number of combination products. And it's difficult to make a guess because a lot of these products don't require inter-center coordination and are reviewed entirely within one center that, over time, has developed certain expertise in that product area. Standard operating procedures are now under review by different centers within the FDA to make intra-agency reviews occur in a more organized and documented fashion."

"The regulatory clock on the request for a designation process used to determine which agency will review a combination product is 60 days," added Kramer. "But at

times submissions need to be supplemented with additional information, or companies request a meeting during the review period because they want to provide additional information. That can cause the total elapsed time to be over 60 days. However, we generally have an agreement with the sponsor to extend the review clock."

Some FDA critics, meanwhile, believe approval times have become too short since FDAMA, and they fear that some manufacturers exacerbate the problem by doing as little testing as possible or by "fudging" clinical data. A scathing July 29 article by *U.S. News & World Report* highlighted past regulatory violations of both Boston Scientific and Medtronic, including withholding important information and details on known adverse events from the FDA. It also pointed out dangers inherent in the 510(k) process and underfunding an overburdened safety-monitoring agency. The FDA's Office of the Inspector General found that, between 1994 and 1999, regulatory violations were far from rare. Device trials were twice as likely as trials for drugs and biologics to violate FDA rules, with such violations including but not limited to missing data, poor data collection, and falsification of data.

Several FDA information sheets have also been put out to offer a needed reminder to investigators and IRBs about the difference between "significant risk" (SR) and "nonsignificant risk" (NSR) device studies – i.e., extended wear contact lenses vs. daily wear lenses. NSR device studies have fewer regulatory controls and do not require submission of an IDE application to the FDA. "The IRB is supposed to make that [SR or NSR] determination," said Stark, "but they've been known to forget." FDA staff was given internal guidance in this area last fall.

Small device firms look for guidance and are respectful of clinical trial expertise once they find it. They are often idea-driven rather than market potential-driven. The entire organization may consist of an engineer, head of regulatory and clinical affairs, and a receptionist. Many folks in the medical device business are naïve and have little relevant experience.

Unless and until something is done to increase FDA resources, the number of required review days on some of the most medically important devices will likely continue to rise. Congress is reportedly looking at an FDA reform package that would give the agency more money to implement process improvements. A program similar to the Prescription Drug User Fee Act is now being implemented for medical devices.

Like pharmaceuticals, there are multiple steps involved in developing a new medical device. Because the product life cycle is much shorter for devices, the time lines for these steps need to be compressed.

The phases can be considered to include the following:

- Prototype design
- Vendor (to provide materials) selection and verification
- Biocompatibility and physical chemical evaluation
- Clinical evaluation
- Regulatory filing and approval

Through the networks of contractors (CROs) to support these steps are less extensive than that for pharmaceuticals, there are still a wide variety of available sources and management issues remain similar.

References

ASTM (1990) Standardization in Europe: a success story. ASTM Standardization News 38
CDRH (1992) Regulatory requirements for medical devices: a workshop manual. Center for Device and Radiological Health, HHS publication FDA 92–4165
FAO (1991) Report of the FAO/WHO conference on food standards, chemical in food and food trade (in cooperation with GATT), vol 1. Rome, 18–27 March 1991
Gad SC (2002) Safety evaluation of medical devices, 2nd edn. Marcel Dekker, New York
Gad SC (2010) International regulatory safety evaluation of pharmaceuticals and medical devices. Springer, Berlin
Kahan JS (2000) Medical device development: a regulatory overview. Parexel, Waltham
MAPI (1992) The European Community's new approach to regulation of product standards and quality assurance (ISO 9000): what it means for U.S. manufacturers. MAPI Economic Report ER-218
MDDI (2000) Industry snapshot. Med Device Diag Ind Dec:47–56
Nugent TN (1994) Health care products and services basic analysis. In: Standard & poor's industry surveys, New York
O'Grady J (1990) Interview with Charles M. Ludolph. ASTM Standardization News 26
Spizizen G (1992) The ISO 9000 standards: creating a level playing field for international quality. Nat Prod Rev, Vol 11, Issue 3, 331–346, Summer 1992
The Wilkerson Group (1999) Forces reshaping the performance and contribution of the U.S. medical device industry. Health Industry Manufacturers Association, Washington, DC
USP (2000) The United States Pharmacopoeia, XXIV § NF-19. U.S. Pharmacopoeial Convention, Rockville