



## Medical Device Development

### From Prototype to Regulatory Approval

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The treatment of cardiovascular disease has changed dramatically over the past 2 decades, allowing patients to live longer and better-quality lives. The introduction of new therapies (both drugs and devices) has contributed much to this success. Nowhere has this been more evident than in interventional cardiology, where percutaneous coronary intervention has evolved in the past 2 decades from a quirky experimental procedure to a therapeutic cornerstone for patients with coronary artery disease. In 2002, approximately 800 000 percutaneous coronary intervention procedures were performed in the United States alone, compared with some 350 000 coronary bypass surgeries. This explosive growth has been fueled by the availability of new devices (guidewires, angioplasty balloons, stents, etc) coupled with validation by clinical data, primarily in the form of randomized clinical trials. However, important differences have evolved in the clinical-regulatory environment between the United States and Europe that have impacted the location of clinical testing and the relative timing of commercial availability. This has led to substantial differences in the speed of introduction and the extent of testing of these devices in the United States and Europe. A prime example of this difference can be seen in the introduction of the drug-coated stent that

became available in European countries 1 year before its arrival in the United States. The Dartmouth Device & Drug Development Symposium was held in October 2003 with joint inventor, entrepreneur, industry, clinical, and regulatory participation, in an effort to characterize the process by which new interventional devices are currently developed and approved. There was also an effort made to identify a series of “sticking-points” in the process, and to suggest some ways in which the efficiency of the process might be improved. This article will review these findings.

#### Invention

Although large medical device companies typically develop successive iterations of existing devices, most new device categories are typically developed by venture-backed start-up companies. Typically, a physician and/or engineer inventor conceives of a device solution to an unmet clinical challenge, initiates the patent process, and builds preliminary device prototypes. Preliminary bench and animal testing may be performed using the inventor’s or an acquaintance’s personal funding (angel investors). Further development typically requires engaging a team of engineers who work closely with physician advisors to bring the concept through the “design-

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build-test-redesign” cycle of bench and animal testing. This preclinical stage typically takes 2 to 3 years and depending on the nature of the device may consume US\$10 to \$20 million before the device is ready for clinical testing. These capital requirements exceed the means of most angel syndicates and are typically obtained from venture capital firms in the form of equity financing.

A small percentage of device ideas are conceived in academic medical centers using federal or other grant funding. Few academic centers have the intrinsic capabilities to develop the device beyond the early prototype stage. Intellectual property is typically out-licensed to an existing company or start-up for further development. To facilitate the development of ideas that emerge out of federally funded programs, Congress passed the Bayh-Dole Act that assigns all intellectual property rights to the academic medical center.

### Initial Clinical Testing

A start-up company’s survival is dependent on reaching milestones efficiently (in terms of time and money) to successfully raise additional funding. First clinical use is perceived by many as a key milestone, so that delays in the initiation of clinical testing programs can threaten a company’s viability. Companies will therefore seek the quickest path to first clinical use. US regulatory requirements are more extensive and require additional time and resources compared with those of other countries. It is estimated that obtaining Food and Drug Administration (FDA) approval to initiate clinical studies in the United States adds 3 to 6 months to the process of device development. In addition, subsequent review by the institutional review board (IRB) at the clinical site can add an additional 3 to 6 months to this timeline. Because of these factors, initial clinical device testing has shifted largely to outside of the United States. It is thus estimated that more than 75% of first clinical use cardiovascular device testing is now outside the United States, saving what may be 6 to 12 months when compared with US clinical initiation. When initial clinical testing is performed within the United States, it is estimated that only 25% of the work occurs at academic institutions. This is due in part to the bureaucracy associated with large academic institutions for both IRB approval and contract negotiations (see below).

Clinical testing of an unapproved significant-risk medical device requires FDA approval in the form of an Investigational Device Exemption (IDE). The IDE application provides information to the FDA on device design and qualification, as well as on the study protocol. The FDA is mandated to respond to the IDE application within 30 days.<sup>1</sup> An IDE may also be required for studies in which an approved device is used for a purpose distinct from its approved indication.<sup>2</sup> This is typically the case when a trial is sponsored by a company for the purpose of expanding the indication of a device or making significant changes in the instructions for use.

### Regulatory Approval Process (United States)

Medical devices are regulated in the United States by the Center for Devices and Radiological Health (CDRH) of the


FDA. The FDA/CDRH mandate is to promote and protect the public health by making safe and effective medical devices available in a timely manner. The standard for demonstrating safety and effectiveness is determined in part by the risk associated with the device in question. Devices are classified according to their perceived risk using a 3-tiered system (class I, II, or III).

Class I devices (lowest risk) are subject to general controls, which are published standards pertaining to labeling, manufacturing, post-market surveillance, and reporting. Devices are placed into class I when there is reasonable assurance that general controls alone are adequate to assure safety and effectiveness. The general controls that typically apply to class I devices include prohibitions against adulteration and misbranding, requirements for establishing registration and device listing, adverse event reporting, and good manufacturing practices. Furthermore, remedies including seizure, injunction, criminal prosecution, civil penalties, and recall authority are provided to FDA. Formal FDA review is not required for most class I devices before their market introduction.<sup>3</sup>

Class II devices are those higher-risk devices for which general controls alone have been found to be insufficient to provide reasonable assurance of safety and effectiveness, but for which there is adequate information available to establish special controls. Special controls may include performance standards, design controls, and post-market surveillance programs. In addition, most class II devices require FDA clearance of a premarket notification application (PMA or 510[k]) before the device may be marketed. In the 510(k) application, the medical device manufacturer must provide data to demonstrate that the new device is “substantially equivalent” to a legally marketed device. Although substantial equivalence can usually be demonstrated on the basis of bench and animal testing alone, approximately 10% of 510(k) applications include clinical data.<sup>4</sup>

Class III devices, such as heart valves, pacemakers/implantable cardioverter-defibrillators, and coronary stents, are judged to pose the highest potential risk. These devices are either life-sustaining/supporting, of substantial importance in preventing impairment of human health, or present a high risk of illness or injury. Consequently, general and special controls alone are inadequate to provide reasonable assurance of safety and effectiveness. Most class III devices require FDA approval of a PMA before they can be legally marketed. Approval of the PMA generally requires clinical data demonstrating reasonable assurance that the device is safe and effective in the target population.<sup>5</sup>

The Human Device Exemption (HDE) is a new pathway to allow for commercialization of class III devices designed to address small markets, ie, diseases or conditions that affect fewer than 4000 patients in the United States each year. Approval of an HDE requires demonstration that the device is safe and the probable benefits outweigh the probable risks. Although the process may require smaller clinical trials, an



HDE device must continue to operate under local IRB approval at each participating institution and must continue to collect case report forms akin to an ongoing clinical trial. The PMA process typically involves a series of studies starting with first clinical use and culminating in a multicenter, prospective randomized control trial (pivotal trial). The complexity and extent of the clinical testing program is dictated by the nature of the device and its proposed use. The clinical study program is developed by the company in conjunction with clinician investigators, all in close collaboration with FDA/CDRH.<sup>6</sup>

The first and arguably most important step in this process is the pre-IDE meeting, in which the company, often accompanied by the lead clinical investigator(s), meets with FDA/CDRH to present data about the device, its clinical development program, and its intended use after approval. The FDA/CDRH staff reviews existing bench and animal data (as well as any outside-the-United States clinical data) and makes informal non-binding suggestions regarding the need (if any) for additional pre-clinical data (bench and animal), as well as the study design. The sponsor then submits an IDE application to FDA/CDRH for formal review.

Clinical development of a new class III device is typically divided into pilot and pivotal trial phases. The purpose of the pilot phase (starting with first clinical use) is to establish safety and to assist in design of the pivotal trial. Pilot-phase testing is typically limited to fewer than 100 patients treated at a few centers. The purpose of the pivotal trial is to generate data that define patient populations in which use of the device is safe and effective. The dialogue initiated during the pre-IDE meeting continues and intensifies between FDA/CDRH and the company over the specifics of the pivotal trial and includes the patient population, the control group against which the new device will be evaluated, and the primary and secondary end points of the evaluation. For first-in-class devices, eg, drug-eluting stents, where there are few data regarding short- or long-term outcomes, FDA/CDRH requires prospective randomized controlled studies. Though high profile, devices that require randomized data for approval are the exception rather than the rule. The vast majority of device clinical trials are case series that carefully document product performance. Still more products are approved as “tools.”<sup>7</sup>

Most devices currently in testing are similar to well-characterized approved devices, eg, next generation bare metal stent, angioplasty balloon, etc. When FDA/CDRH has substantial data on the device class metrics, comparisons may be made to historical data or objective performance criteria. When few data on existing standards are available, the FDA typically requires randomized rather than single-arm studies, in which the new device is compared against concurrent controls treated with current best medical practice. That comparison may be powered to show that the new treatment is superior to prior approaches, or that it is non-inferior (equivalent or better) compared with a previously approved

device in a new area. The issues relating to the type of trial are discussed below.


The specifics regarding study design may have profound impact on the time and cost of bringing a new device to market. Though the primary mission of the FDA/CDRH is to ensure safety and effectiveness of commercially available devices, when exerting regulatory oversight the agency must balance its primary mission with the costs of introducing new technologies to the clinical marketplace. This has been codified by the FDA Modernization Act and the FDA Modernization Act-II, which require the agency to pursue the “least burdensome means” available to establish device safety and efficacy.<sup>8,9</sup> Although surrogate end points, eg, angiographic restenosis rather than recurrent cardiac events, may be allowed as secondary end points, the primary end point of a pivotal trial for a first-in-class class III device is usually a clinical end point (or a well-established surrogate such as infarct size in a myocardial infarction treatment device). Depending on the end points negotiated, such pivotal trials may require enrollment of 1000 or more patients at 30 to 50 sites over a period of 1 to 2 years, with appropriate follow-up frequently to 1 year after treatment. The trial must be conducted according to good clinical practices standard, with the approval of the local IRB at each participating center.

### **Clinical Site (IRB, Contract, Conflict of Interest)**

Once the FDA/CDRH has approved the IDE, the sponsor must formally recruit as many as 50 sites to ensure patient enrollment in a timely fashion. Each site has its own rules regarding participation in clinical studies, which typically can be divided into 3 components: Human research, contract, and conflict of interest.

Every clinical site is federally mandated to have an IRB responsible to ensure the protection of the rights, safety, and welfare of research subjects. Regulation of the IRB review of protocols involving medical devices is under the purview of the FDA. The Office of Protection From Research Risks (OPRR) is responsible for oversight regarding all human research and is in direct communication with the FDA/CDRH. Studies involving human subjects that do not involve products regulated by the FDA fall under the direct purview of the OPRR. Both the FDA and the OPRR are in the Department of Health and Human Services. Each IRB must meet standards for the composition, leadership, and processes set forth by that department. IRBs are subject to periodic audits by the FDA to ensure that records and procedures are in compliance with regulations.<sup>9,10</sup>

Working with the sponsor, the principal investigator prepares an application to the IRB at his/her institution that includes the consent form describing in lay language the device, the proposed clinical study, the inclusion and exclusion criteria for the trial, and a draft consent form describing the risks and benefits of participation in the study. The IRB then formally reviews the application and frequently requests



changes, particularly to the informed consent. The IRB process typically requires approximately 3 months, but at times can take considerably longer.

The company must also negotiate agreements with each clinical site addressing the many issues associated with the clinical trial. In addition to the study costs/reimbursement (per-patient enrolled and overhead), these agreements typically include indemnification and the assignment of ownership rights of new discoveries (intellectual property) made in the course of the study. The resources required at each center to perform the high quality research necessary for a PMA protocol are formidable. In addition to resources required to maintain an excellent clinical program (physician, nursing, and technical staff coupled with state of the art facility), the study center must dedicate additional resource, primarily research nurses to perform high-quality clinical research. The role of the research nurse is critical to all phases of the trial, including general study management, IRB process, patient recruitment, and accurate completion of case report forms. The sponsor is responsible for accrediting each clinical site to document that the necessary resources are in place to fulfill the demands set forward in the protocol. The clinical research staff do not provide clinical care and are thus not part of the hospital's salaried clinical nursing staff. The per-patient costs include all additional charges the patient incurs for the study, including procedures (therapeutic and diagnostic), clinic visits, and diagnostic studies, as well as research nurses' salaries. It is estimated that it takes 3 to 6 months to formally recruit each clinical site.

Device development from the earliest stages requires active involvement of practicing clinicians. Clinician/inventors are frequently involved in creation of the device concept and are often integral members of the design team performing the majority of the early animal studies. Through this involvement, the clinician/inventor obtains intimate knowledge of device performance and failure modes. Safety concerns during first clinical use and pilot phase mandate participation by these clinician/inventors. The clinician/inventors frequently take leadership roles and have equity positions in the company developing the device. These interests present important conflicts of interest which must be addressed to ensure patient safety, data integrity, and public trust in the process. Many institutions have set up formal processes to address these conflicts of interest, potentially adding more time to the institutional recruitment process.

Pivotal studies required for a PMA application are typically large multicenter randomized trials and often represent the largest commercial risk and expense in the device development process. In addition to obtaining an IDE from the FDA and formally recruiting clinical sites, the sponsor must also put into place an extensive infrastructure that typically includes engaging a contract research organization (CRO), core laboratories, formation of a data safety monitoring board (DSMB), and an executive committee. The CRO provides the infrastructure required to recruit, qualify, and

audit sites. Core laboratories evaluate primary data, eg, angiography, ECG, and ultrasound results, in a uniform and blinded manner. An executive committee is typically composed of the clinician investigators, company representative, CRO, and core laboratories. The DSMB, composed of a group senior clinical investigators and statisticians with no other involvement in the study, periodically reviews trial data at specified intervals. The DSMB has the mandate to stop or modify a study, eg, discontinue randomization to one of the groups if complications associated with the study device are in excess of anticipated rates, if differences between study groups reach statistical significance, or if further patient enrollment will not impact study outcome.

### Regulatory Approval Process (European Union)

Though there are many similarities in the regulatory process in the United States and countries within the European Union, there are important differences that impact the time and cost associated with the introduction of a new medical device. We have identified 3 illustrative examples: Use of notified bodies, criteria for approval, and local site (IRB/site negotiation).

The European Union system relies heavily on notified bodies (NBs), which are independent commercial organizations to implement regulatory control over medical devices. NBs have the ability to issue the CE mark, the official marking required for certain medical devices. NBs are designated, monitored, and audited by the relevant member states via the national competent authorities. Many functions performed by the FDA/CDRH within the United States are performed by NBs, including medical device certification, device type designation, assessment and verification of quality systems, and review of design dossiers for high-risk devices.<sup>11,12</sup> Currently, there are more than 50 active NBs within Europe. A company is free to choose any notified body designated to cover the particular class of device under review. After approval, post-market surveillance functions are the responsibility of the member state via the competent authority. NBs typically function in a closed manner, providing little visibility on criteria required for approval. This dynamic allows for a high degree of variation as well as competition among NBs. As a result, NBs are perceived by industry to be less bureaucratic organizations that can respond more quickly and efficiently than the FDA. These potential benefits may be offset by a system that is intrinsically more fragmented and highly variable and has resulted in the approval and continued marketing of devices, eg, abdominal aorta stent grafts, in Europe that failed efficacy trials in the United States.

Criteria for approval of high-risk devices are different in the European Union. To receive approval to market a class III high-risk (and some class II) device in the United States, the manufacturer must demonstrate the device to be reasonably safe and effective, which typically requires a prospective,

randomized controlled clinical trial. To receive approval to market a device in the European Union, the manufacturer must demonstrate that the device is safe and that it performs in a manner consistent with the manufacturer's intended use.<sup>12</sup> This difference has a profound impact on the size and scope of the clinical studies for regulatory approval. This significant difference is illustrated by examining the introduction of distal protection systems. The GuardWire developed by PercuSurge, Inc (later acquired by Medtronic) is a specialized coronary guidewire with an elastomeric balloon mounted at the tip. During an angioplasty/stent procedure, the operator crosses the lesion with the GuardWire and inflates the balloon. Stent placement is then performed, after which a specialized catheter is used to evacuate any arterial debris that may have become dislodged during the procedure. The GuardWire balloon is then deflated. Demonstration of safety and performance, ie, ability to aspirate material during the stenting procedure, was demonstrated in a 22-patient single-arm study.<sup>13</sup> In contrast, in the United States, this device was designated class II (requiring 501[k] clearance and clinical data). To satisfy US criteria for clearance, the standard of safety and effectiveness required in this case was defined as the ability to reduce complications associated with stenting of saphenous vein grafts. To meet this criterion, an 800-patient multicenter trial randomized trial comparing distal protection to usual care (no protection) was performed. At 30 days, a 42% relative reduction in major adverse cardiac events (primarily myocardial infarction) was observed.<sup>14</sup> A trial of this type is estimated to cost US\$10 to \$12 million and may take 24 months to perform.

### Conclusion

As this review highlights, the demonstration of safety and efficacy for a new medical device is a long, arduous, and expensive developmental path from early concept to introduction into clinical practice. Only by understanding this path and its complexity may we hope to make the most efficient use of this critical process and allow the timely introduction of important new devices into our therapeutic armamentarium. The above review outlines this process and highlights some of the differences in the clinical and regulatory environments in the United States and Europe. Understanding these differences, moreover, helps explain why much early device testing takes place outside of the United States, and why the introduction of new devices into clinical practice is usually significantly delayed in the United States when compared with Europe. Both phenomena are direct results of inherent differences in the criteria for approval and the process required to obtain approval. In particular, the European CE Mark process requires demonstration of safety only

(and not efficacy) and relies heavily on non-governmental notified bodies to regulate the approval and post-approval process. In contrast, the approval of a new high-risk device in the United States requires demonstration of both safety and efficacy and is more highly regulated by a central governmental agency (CDRH/FDA). Even when the FDA has authorized early US clinical trials, clinical testing must pass significant additional hurdles at each clinical site in terms of IRB and contract approvals. This process has become significantly more arduous in the wake of recent misadventures in drug and gene therapy testing.

Taken together, these factors account for the 1- to 3-year delays in the introduction of new device technologies into general clinical practice within the United States as compared with Europe. Each system has strengths and weaknesses that must be evaluated within the context of different health delivery systems. Through better understanding of these systems, will we be able to recommend modifications and improvements toward improving speed and efficiency (shorter delay to US versus European testing and ultimate clinical approval), without compromising the basic demonstration of safety and efficacy that remains the US regulatory mandate.

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