The past 60 years have witnessed fundamental advances in our understanding and treatment of cardiovascular disease, prolonging and improving patients’ lives. Central to these improvements has been the introduction of medical devices, including mechanical and biological heart valves, heart rhythm devices, and balloon angioplasty and stents. The introduction of these technologies has been dependent on an entrepreneurial medical device sector, coupled with an equally robust infrastructure to clinically develop and evaluate these new technologies. After approval and commercialization, continued study of device performance under “real world” conditions is crucial to ensure that the clinical potential is being realized.

Central to a healthy medical device “ecosystem” is a robust regulatory system. Regulators must ensure that a device performs reliably and is adequately characterized, allowing physicians and patients to use it appropriately. Determining if/when a device is appropriate for approval is difficult and challenging and requires balancing its safety-efficacy profile. The technical sophistication required to make these determinations has grown as device complexity has grown. The stakes are very high, as illustrated by the recent Fidelis AICD lead recall, affecting 268,000 patients worldwide.\(^1\)

These safety concerns must be balanced by the harm inflicted by withholding beneficial technology from patients. There is wide variation in how devices are regulated among countries with well-developed health care delivery systems, for example, the United States and Europe as well as Japan and Canada. The recent Food and Drug Administration (FDA) approval of the Sapien Transcatheter Heart Valve has brought these differences into sharp focus. In this commentary, we review the differences between the US and European Regulatory systems and how they have affected the investigational and approval process.

Sapien Transcatheter Heart Valve: A Case Study

On November 2, 2011, the Sapien Transcatheter Heart Valve (TAVR), manufactured by Edwards Lifesciences, was approved by the US FDA.\(^2\) The approval of the Sapien Valve heralds the arrival of a truly breakthrough treatment that has been shown to reduce death in patients unable to undergo conventional surgical valve replacement.\(^3\) Despite the magnitude of this salutatory treatment-effect, the United States was the 40th country to approve the TAVR and followed approval in Europe by more than 4 years. The lack of access of this technology has been the source of significant frustration for patients, their families, and clinicians.

The emergence of the medical device sector has in large part been a US phenomenon hatched by engineers, clinicians, and entrepreneurs working within small companies typically funded by venture capital firms. When technology with potential to address a significant market need demonstrates proof of concept, it is often acquired by large established device manufacturers who leverage their manufacturing, clinical development, and marketing expertise as well as provide the large capital required for further development. The development of TAVR is illustrative of this sequence.

The success of the early TAVR experience has caught the attention of many innovators who have been able to attract investment to develop next-generation valves and associated technologies. These next-generation technologies will no doubt dramatically improve on currently available TAVR technology. For patients to realize the benefits of these efforts, an efficient process will be required to evaluate and commercialize these devices.

US Regulatory Process

US regulatory responsibility for medical devices resides with the Federal Government through the FDA Center for Device and Radiological Health (FDA/CDRH).\(^4\) The TAVR is categorized by FDA/CDRH as a class III significant risk device, which requires demonstration of safety and effectiveness for approval as part of the premarket approval (PMA) process. The PMA process can be broken down into 4 basic stages.

Pre–Investigational Device Exemption/Preclinical Evaluation (Stage I)

The PMA process is initiated by the medical device company with a series of meetings with FDA/CDRH focused on preclinical (bench and animal) testing as well as plans for a clinical trial. The extent and duration of these tests is the focus of the early pre–investigational device exemption (IDE) meetings. Seemingly small changes in these requirements, for example, duration of chronic animal studies (3 versus 6 months), can have a large impact on capital and time required to initiate clinical testing.
When the sponsor has completed the agreed upon bench and animal testing, a formal IDE application is filed. The IDE application is a comprehensive several thousand-page document which includes device rationale, preclinical (bench and animal) test results, clinical data from outside the U.S., instructions for use, and the clinical test protocol. IDE filing starts a formal review process, to which the FDA provides comments and the sponsor replies. Though variable, IDE approval typically requires 3 or more cycles. IDE approval comes when FDA/CDRH is satisfied that (1) preclinical evaluation demonstrates the device is appropriate for clinical use and (2) the clinical study will generate data capable of supporting a PMA. IDE approval may take as long as 1 year.

**IDE/Clinical Testing (Stage II)**

The clinical research community gets involved when clinical sites are recruited to participate in the study. The sponsor negotiates agreements at each clinical site, which includes study fees and other issues including indemnification, which is often problematic. In parallel, ethical review of the protocol by the institutional review board (IRB) for each clinical site is undertaken. Depending on the site, IRB review can be protracted. Finally, Centers for Medicare and Medicaid Services (CMS) approval is also required when treating Medicare patients. This latter process has recently been decentralized, requiring the sponsor obtain approval from the chief medical officer in each region. In aggregate, this process takes about 6 months for most sites but can take as long as 12 months.

To ensure high-quality data, device clinical trials are performed according to Good Clinical Practices, which typically includes formal site initiation and auditing, core laboratory data analysis, independent data management with events adjudicated by a formal clinical events committee, and review by a data safety monitoring board. These adjunctive but essential activities require a vast infrastructure, making these studies very expensive. Given the need to address a specific scientific question, early approval trials limit enrollment to only highly selected patients. This restriction results in extended time for trial completion and also raises questions regarding the ability to generalize trial findings to the larger population of patients who might be treated with the new technology.

**Data Review–PMA (Stage III)**

After trial completion, the data are “scrubbed and locked” and then unblinded. If the study is positive, a PMA application is prepared by the sponsor and submitted to FDA/CDRH. The PMA application is a comprehensive set of documents that includes the preclinical and outside the United States data submitted to support the IDE as well as a complete analysis of the study data. The FDA/CDRH review process can take as long as 12 months and may culminate in a presentation to an FDA advisory panel. After the advisory panel’s review, the FDA/CDRH makes its final determination and will stipulate specifics of the indications statement as well any postapproval studies that might be required.

**Postmarket Approval (Stage IV)**

After approval, the sponsor is subject to the “special controls” regulations required under Good Manufacturing Practices guidelines for the manufacture of medical devices. FDA surveillance includes regular inspections to ensure compliance. In addition, as in the case of TAVR, the FDA works with the sponsor to develop a plan that may include specifics regarding site/physician training, postmarket surveillance registries, and studies. For TAVR, postmarket studies were done within the context of testing the next-generation iterations of the TAVR.

**European System**

The European medical device regulatory system differs in important ways from the United States and has a profound impact on the time and investment required to obtain approval. Approval times achieved in Europe are quicker than in the United States and are largely due to the use of notified bodies (NB) as well as different approval standards.4,5 NBs are typically private, commercial entities recognized by European Union Member States. Medical device companies chose 1 of the >75 NBs to evaluate a specific product(s) for CE Mark approval.6 The CE Mark allows a device manufacturer to market their product throughout the European Union. This system has been criticized for allowing the manufacturers to shop for the most lenient NB, wide variation, lack of transparency, and the conflict of interest generated by the manufacturer paying the NB directly.5,6

Regulatory oversight of clinical investigation with unapproved devices resides with competent authorities of each member state or country. As might be anticipated, this system results in a variation of how and what devices are approved among different European countries. Ethical approval is obtained by a medical ethics committee, which is typically done regionally.

Similar to the FDA/CDRH process outlined above, the sponsor works with the selected NB on the specifics of the preclinical and clinical testing requirements required for CE mark. European requirements require demonstration that the device is safe and performs in a manner consistent with the manufacturer’s intended use. Furthermore, a risk/benefit analysis is provided. This approach differs markedly from the United States, where demonstration of safety and effectiveness within the context of a specific indication is required. Accordingly, the European system typically does not require statistically powered, randomized, controlled studies for the approval of a first-in-class, high-risk device. When compared with the US standard (safety and effectiveness), the European standard (safety and performance) markedly reduces the size and scope of the clinical trial(s) required for approval. In the case of the Edwards Sapien valve, European approval was obtained with an aggregate of data from 500 patients in feasibility and single-arm registries, without randomized, controlled data.7

**Implications**

**Patients Are Denied Proven Life-Prolonging Technology**

The results of the Partners B Trial, comparing the Sapien valve to medical therapy alone, are quite compelling, demonstrating a mortality reduction from 50.7–30.7%, representing a relative 39% reduction (P<0.001).8 Patients without access to this technology can expect 20% excess mortality at
1 year. Furthermore, the current enthusiasm created by the recent approval obscures the fact that US patients will only have access to “first-generation” technology, which is significantly larger and more difficult to deliver when compared with “second-generation” technology currently in use outside the United States. As with the first generation, the FDA is requiring a large, randomized, controlled trial to evaluate the long-term durability of the “second-generation” valve/delivery system. This means US patients can expect more untoward complications related to vascular access than European patients.

Delay in Development of Clinical Expertise and Infrastructure
The delay in access to TAVR technology places our innovation and product development at a disadvantage. The lack of clinical experience prevents US clinician-inventors from obtaining the intimate knowledge of the technology that is essential to identifying and developing next-generation technology.

Early device evaluation is rarely performed in the United States. The FDA requires all standard pre-IDE testing even for a limited feasibility study. In addition, US sites are more expensive and typically require more time to negotiate contracts and secure IRB approval. Quite simply, US sites are less competitive than European, Asian (New Zealand and Australian), and selected South American sites, where the majority of early device evaluations are currently performed.

European System Is Not a Panacea
Though the European regulatory process is more efficient than in the United States, it is important to acknowledge its deficiencies. Many have criticized the European system with regard to standards for the approval for drug-eluting stents. Currently there are more than 20 different approved drug-eluting stents in Europe, many of which are poorly characterized with respect to late and very late thrombosis.

It also must be acknowledged that the European regulatory approach works in part because the majority of high-impact devices will undergo the more rigorous, subsequent evaluation as part of the US approval process. In fact, the European medical device regulating approval process is currently under review, in part to assess if more stringent premarket clinical data requirements should be put into place.

Path Moving Forward
As we learn from the TAVR example, we must balance the imperative of bringing new technology to the clinic while acknowledging the harm caused when unsafe technology is approved and widely adopted.

We propose 4 areas for streamlining the regulatory process described as follows.

Support for a Strong, Independent FDA/CDRH
There is no doubt that a strong FDA/CDRH, which is consistently funded, able to attract best-in-class staff with deep technical expertise, and provide long-term continuity, is fundamental to a healthy medical device “ecosystem.” As such, advocating for consistent funding at the congressional level as well as taking a collaborative and collegial tone when dealing with our FDA/CDRH colleagues are both imperative.

Also, the public must be aware of the benefits of a healthy medical device “ecosystem,” which has contributed to the health of the US population as well as supported US leadership in the medical device sector. Percutaneous coronary intervention for acute myocardial infarction is an example.

Continuity Between PMA and Postmarket Approval
As stated above, finding balance when making approval decisions is difficult in large part because of the lack of comprehensive understanding of how a device will perform after general release. This problem is magnified by the dichotomous nature of the approval decision, which makes further evaluation, especially in the form of randomized, controlled trials, difficult if not impossible. In addition, the ability of the FDA/CDRH to rescind approval of an appropriately manufactured device is nearly impossible.

We propose to consider a 2-step approval system in which “initial approval” (time-limited) is provided on the basis of safety and performance, similar to current standards within the European Union Systems. Subsequent “final approval” will require demonstration of safety and comparative effectiveness, using current standards. The clinical study plan will be mapped out at the time of initial approval. This proposal will need further review and vetting and probably will require legislation to implement.

Centralize the CMS Approval Process
As outlined above, one of the impediments to performing clinical investigation in the United States includes the recent regionalization by CMS of approval for funding of IDE coverage decision. We suggest a central office, so that sponsors can work through all issues associated with a specific trial at one time.

Focus on Early Device Investigation
Though the majority of large medical device manufacturers are US-based, they are globally focused and as such seek clinical investigative sites that are the most competitive and strategic. US clinical sites have lost all of their advantages and will have to work to regain competitiveness. Efforts are currently underway at the FDA/CDRH to streamline the IDE process to facilitate having early clinical feasibility trials performed in the United States. Similar efforts are needed to address the other barriers that limit our competitiveness, including slow IRB response, arduous contract negotiations, and repetitive efforts at CMS.

Acknowledgments
This work emanated in part from discussions held at the 9th Dartmouth Device Development (3D9) Symposium held on Sept. 22nd and 23rd, 2011 in Hanover, NH.

Disclosures
Dr Kaplan is a founder and director of Tryton Medical, Inc, a venture back start-up company developing a bifurcation stent. Dr Kaplan has
received research funding from Johnson & Johnson, Abbott Vascular, Medtronic, Boston Scientific, and Edwards Lifesciences.

References

Key Words: transcatheter medical device regulation
Medical Device Regulatory Landscape: The Imperative of Finding Balance
Aaron V. Kaplan and David O. Williams

doi: 10.1161/CIRCINTERVENTIONS.112.968560
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circinterventions.ahajournals.org/content/5/1/2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Interventions can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Interventions is online at:
http://circinterventions.ahajournals.org/subscriptions/