Medical Technology Development and Approval

The Future Is Now

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Alvin Toffler, a 20th century philosopher and author of the novel *Future Shock* once said, “As we move into the 21st century, not only will technology advance, but the rate at which technology advances will increase exponentially.”1 Perhaps those technological advances with greatest relevance to the health and welfare of society involve science and healthcare. Indeed, societal demands for new drug and device design and development have never been greater. Because of advances in medical care, the mortality from cardiovascular diseases has progressively declined over the past 2 decades. We currently stand on the threshold of “cures” for several of mankind’s greatest afflictions, including cancer, atherosclerotic cardiovascular disease, and human immunodeficiency disease.2 Obviously, the time efficiency of providing potentially life saving technologies to society is crucial—lives literally depend on this process. Ideally, benchmarks for safety and efficacy of technology should be satisfied before drug/device availability to assure net clinical benefit. The “gatekeeper” for medical technology is the United States Food and Drug Administration (USFDA), whose charge it is to promote and protect the public health by making safe and effective medical technologies available in a timely manner. Furthermore, in the current era of escalating costs for medical technology, the time required for the development–FDA approval–release process (“time to market”) translates directly into drug/device pricing. In recent years, as cardiovascular specialists, we have been fortunate to be provided with both primary preventative therapies (aspirin, statins, angiotensin-converting enzyme inhibitors, etc) that reduce the prevalence of cardiovascular disease, in addition to exciting new technologies (implantable cardiac defibrillators, cardiac resynchronization therapy, drug-eluting stents, etc) that substantially reduce the morbidity and mortality for those in whom this disease is established.

As clinical investigators for new technologies, we are acutely aware of a widening time gap between the availability of US industry-developed technologies in Europe or other countries outside the US and the United States itself. Concern exists that a bureaucratic process should not disadvantage the US public by stifling timely access to new or improved medical technology. Probably no other single topic more effectively aligns the incentives of all interested parties, including the US public, physician investigators, industry, and the USFDA. Close collaboration between physician investigators, industry, and the USFDA is essential to effect enhanced efficiency in the process of device development, USFDA approval, and release, while still maintaining a premium on public safety. Such a collaborative effort is made evident in the current issue of *Circulation* by Aaron Kaplan, MD, et al.,3 who describe in detail the current process by which new medical devices are developed, undergo clinical testing, and are evaluated by the USFDA. In addition, a consensus proposal for improving our current system is provided in the accompanying work by Mehran et al.4

The Present

An accurate understanding of the US regulatory approval process and its components from first-in-man clinical testing,
FDA investigational device exemption, and pivotal trial evaluation through pre-market approval application submission and FDA approval is provided in the work of Kaplan et al. In addition, the comparable regulatory process in European Union (EU) countries is described. Basic fundamental differences between the US and EU processes include the use of independent commercial organizations (notified bodies) to implement regulatory control, as well as a primary focus on device safety rather than proven efficacy in the EU system. A conceptual understanding of both the potential advantages and pitfalls of the EU system are important in objectively assessing the US regulatory process and in devising strategies for improvement. Indeed, in the article by Mehran et al., a more comprehensive and integrated approach to new device development and approval is proposed. The concept of effective post-market surveillance to facilitate pre-market approval is intuitively attractive. Furthermore, Mehran et al outline the inadequacies of the current US post-market surveillance system. Clearly, substantive improvements in the post-market surveillance process are prerequisite for implementing the proposed strategy.

In return for the privilege of more timely availability of technology, physicians, healthcare institutions, and industry have a joint responsibility for more accurate, systematic, and comprehensive new device surveillance. The current medical device reporting program is woefully inaccurate and incomplete. Furthermore, a mechanism for systematic audit must be in place to assure both accuracy and completeness of the data compiled. Quality-assured data on device safety and clinical efficacy over time in large, diverse patient populations would be invaluable to the understanding of a new device’s impact on a specific disease state. The availability of such data could substantially enhance the adoption of a technology for new indications, as well as for the current FDA “labeling” process. These data, by virtue of their magnitude, could materially influence the development and continuous quality improvement cycle of clinical practice guidelines for device use. Clearly, one cannot underestimate the potential importance of a large-scale, quality-assured clinical database that includes long-term follow-up post-device utilization as part of a continuous quality-improvement feedback loop to clinical practice. Obviously, the integrity of the data is essential and current disincentives for physicians who encounter adverse events in the course of off-label device utilization must be overcome.

The Future

The proposal of Mehran and colleagues represents an important first step in the evolution of our current regulatory process. A step, they believe, that will enhance the efficiency of our current system without jeopardizing its safety. Indeed, the database they propose to develop addresses glaring deficiencies in our current regulatory and healthcare systems. It is remarkable that we have come to the present point in time without a reliable mechanism in place to track and monitor new device utilization. A case study in point is provided by both Kaplan et al. and Mehran et al. in the Cypher drug-eluting stent. In an initially limited and select randomly assigned patient population, this device demonstrated remarkable effectiveness and safety in reducing restenosis and the requirement for repeat coronary revascularization when compared with conventional coronary stenting. Nevertheless, specific comments regarding the Cypher stent made during the course of the FDA panel evaluation or after approval are noteworthy. For example, in reference to the pivotal US trial of this device in 1100 patients randomly assigned to treatment with either Cypher or BX Velocity stents, Mitchell Krucoff, MD, of the FDA panel queried, “What is the beta error level for a 1000 patient randomized study? Could we miss a 1% adverse outcome?” Indeed, the potential for missing a low frequency occurrence adverse outcome even in the course of a pivotal trial on which USFDA approval is contingent is evident, and yet could become quite obvious by extrapolation to the >600 000 patients/year who undergo coronary stent implantation in the United States. The mechanisms currently available for device surveillance, as well as their limitations, are succinctly summarized by Mehran et al. A dependable, comprehensive post-market surveillance system may have reduced the subsequent sensational revelation of the potential propensity for Cypher stent thrombosis, as well as the consequent USFDA response to a non-event. Similarly, an accurate assessment of the impact of this revolutionary device technology on clinical practice was in large part missed. Access to quality, clinical data in an expanded patient population might have allowed practicing physicians to more rapidly and confidently extend use of this device to patient subsets not included during randomized clinical trial testing. As aptly queried by established physician investigators, “should standard practice patterns undergo marked immediate changes when fewer than 2000 patients have been studied in 3 clinical trials?” (before Cypher stent USFDA approval). These issues are not likely to be solved simply by integrating currently available, fragmented data sources from Medicare/third party claims made, device specific registries, or society databases. Little or no assurance of accuracy or completeness exists even if Health Insurance Portability and Accountability Act–compliant integration of these data sources were to occur. A more accurate and comprehensive system is required to assure safety and efficacy of new technologies. Support for a new post-market surveillance system could be provided through collaboration and consolidation of resources currently allocated to our fragmented and less comprehensive data sources, as well as by a portion of industry profits derived from expedited device approval, if achieved. Indeed, “time to market” can be worth $1 million per day to industry.

The proposal by Mehran and colleagues is in response to the current 1- to 3-year gap for introduction of new device
technologies in EU countries and the US, respectively. Although attractive and ultimately quite informative, this proposal will no doubt be challenging and costly to implement. The information technology is currently available to accomplish this goal if political barriers and self-interest of stakeholder parties can be overcome. These potential obstacles must be subjugated by the willing collaboration between clinical investigators, industry, and FDA regulators in the best interest of our patients.

References