FDA Response to Medical Device Regulatory Challenges

A description of initiatives designed to expedite the review process.

BY DOROTHY B. ABEL; ANDREW FARB; AND MEGAN MOYNAHAN

Critiques of medical device regulatory systems typically present one of two conflicting viewpoints: (1) arduous regulatory requirements delay or prevent beneficial device availability; and (2) less rigorous regulatory requirements put citizens at risk of being exposed to hazardous or ineffective devices. Often, the assessments of device regulation are supported by analyses comparing the US Food and Drug Administration (FDA) policies to the European Union regulatory process, seemingly with the goal of identifying the better system and suggesting an overhaul of the "inferior" system to mirror the other. Unfortunately, this approach is no more useful than trying to identify a single optimal vascular intervention among countries without considering their disparate economies, cultures, and medical systems.

In reality, there are trade-offs in every regulatory system, with advantages and disadvantages that have shared foundations. The United States system is often characterized as one that succeeds in keeping ineffective devices off the market, but in doing so, also delays access to new effective devices. In contrast, the European Union system appears to allow earlier access to devices in which safety and effectiveness are characterized less rigorously, but allow more rapid removal of products from the market, when appropriate.

When assessing the need for regulatory reform, a fundamental consideration is whether patient care is better when there are more available treatment options with less available supporting data or when there is more evidence available on fewer treatment options. Addressing this issue for any regulatory system requires attention to the particular medical ecosystem that includes the patients', physicians', hospitals', and the public's tolerance for risk, along with the consideration of multiple metrics, not only time to market.

In assessing any regulatory system, the often conflicting views of the public need to be considered. When faced with limited treatment options for some diseases and conditions, patients desire early access to novel devices and bemoan not having choices. At the same time that they embrace medical progress, they may be unwilling to sacrifice an assurance of safety. Patients may also be skeptical of device manufacturers' business priorities and have substantial concerns regarding potential biases associated with perceived conflicts of interest. Additionally, individual physicians and hospitals can be wary of the legal liabilities associated with the use of unproven technologies.

Although the pendulum of public opinion and regulatory responses swings between risk tolerance and risk aversion, there is a growing sentiment that the current regulatory system is stifling device innovation in the United States. Beyond delaying access to highly novel technologies, it is perceived that the United States regulatory environment inhibits the evaluation of, and subsequent approval of, even modest improvements to existing technologies.

This article describes conceptual production and innovation models as applied to FDA device regulation and lists previous efforts to improve device regulation in the United States. Some of these reforms have been made within existing medical device legislation, whereas others have been mandated through new federal laws. The article acknowledges continued limitations of the system and presents ongoing efforts to address outstanding challenges within the confines of the current laws.

TABLE 1. MAJOR SUBMISSIONS RECEIVED DURING FISCAL YEARS 1999 TO 2009

Type of Submission	1999[a]	2000[a]	2001[a]	2002[a]	2003[a]
Original PMAs	64	67	71	49	54
PMA supplements	557	546	641	645	666
Original IDEs	304	311	283	312	242
IDE supplements	4,127	4,388	4,810	4,722	4,415
510(k)s	4,458	4,202	4,248	4,320	4,247
Original HDE	12	11	5	5	10
HDE supplements	4	10	16	16	29
513(g)s	43	59	82	104	156
Total	**9,569**	**9,594**	**10,156**	**10,192**	**9,819**

[a]ODE and OIVD.
[b]ODE only.

MEDICAL DEVICE PREMARKET REGULATORY SUBMISSIONS

Office of Device Evaluation (ODE) personnel in the Center for Devices and Radiological Health (CDRH) spend the majority of their time reviewing documents submitted by industry or physicians. These submissions include investigational device exemption (IDE) applications that allow for the clinical study of significant-risk devices in the United States, 510(k) submissions for devices that can be found to be "substantially equivalent" to legally marketed devices, and premarket approval (PMA) applications that include information intended to provide reasonable assurance that a device is safe and effective.

Based on the fiscal year 2009 annual report (http://bit.ly/FDAannualreport2009), the ODE receives almost 10,000 premarket submissions each year, including 510(k)s, PMAs, and IDEs, as well as IDE and PMA supplemental applications, requests for designation, presubmissions, and humanitarian device exemption (HDE) applications (Table 1). Conservatively, probably fewer than 200 of these annual submissions are for innovative devices or novel clinical uses, considering the total number of original IDEs, HDEs, and PMAs received. This estimate takes into account that most IDEs and PMAs are for "me too" devices and that IDE and PMA supplements tend to be submitted for iterative device changes. Also, devices that are reviewed under the 510(k) system tend not to be highly innovative because, by definition, the 510(k) process involves showing that the new device is not significantly different from a legally marketed device.

THE UNITED STATES DEVICE REGULATORY SYSTEM AS A PRODUCTION MODEL

Factories utilize production models to mass produce, efficiently meet customer demands, drive down costs, drive up value, and, through a process of incremental improvement, steadily bring forward better products and service to customers. CDRH's "products" are regulatory decisions based on the evidence provided in the applications. In order to efficiently manage the large number of applications, which cover a wide spectrum of medical device types, the ODE has created a production model that relies on the use of standardized operating procedures.

The production mindset is efficient for both the FDA and manufacturers. However, the model requires continued maintenance and evaluation to remove inefficiencies, use better metrics, be more responsive, improve transparency, and optimize the predictability of the regulatory process. Past efforts have included the following actions:

- In 1998, the New 510(k) Paradigm provided the option of submitting "Special 510(k)s" that allowed a manufacturer who modified their own marketed device to submit less information than would be required for a traditional 510(k) by leveraging design control requirements.
- Compared to a traditional 510(k), a Special 510(k) takes approximately one-third of the review time.
- The pre-IDE program was initiated in 1995 and was further refined in 1999. This program allowed interaction with a sponsor prior to the submission of a formal IDE in order to improve the probability of a first-round IDE approval.
- Beginning in 1997 and modified in 2006, the Real-Time PMA Supplement was introduced, which allowed approval of certain types of changes to a marketed device using an interactive review process. As compared to traditional PMA supplements, Real-Time supplements take approximately one-third of the review time.

	2004[b]	2005[b]	2006[b]	2007[b]	2008[b]	2009[b]
	37	43	25	31	26	20
	565	712	1,113	1,087	1,448	1,394
	222	226	251	211	216	222
	4,297	4,264	4,485	4,345	4,409	4,281
	3,107	3,130	3,240	3,192	3,363	3,597
	9	4	4	6	3	3
	28	24	53	23	40	40
	239	287	244	381	96	98
	8,504	**8,690**	**9,415**	**9,276**	**9,601**	**9,655**

Abbreviations: OIVD, Office of In Vitro Diagnostic Device Evaluation and Safety (Note: the name of this office is now the Office of In Vitro Diagnostics and Radiological Health).

Although these efforts resulted in measurable improvements in approval times for some submissions, additional changes were warranted. In response to increasing demands to improve regulatory science and to shorten timelines, a pay-for-performance system of user fees under the Medical Device User Fee and Modernization Act was established in 2003. In a letter from the Secretary of Health and Human Services to Congress, the FDA committed to meeting certain review performance goals in return for increased funding paid directly by the regulated industry. The rules introduced new metrics for evaluating the time it took to reach a regulatory decision, such as approval and not-approvable, and held CDRH to shorter review times for PMAs and 510(k)s. In 2008 and 2012, the performance goals were further refined as part of the Food and Drug Administration Amendments Act of 2007 and the Medical Device User Fee Amendments (MDUFA) of 2012, now referred to as MDUFA II and MDUFA III, respectively.

Despite a modicum of meaningful progress, more work is needed in the production model to optimize its performance. As FDA-regulated medical products become increasingly complex, there are persistent complaints about increased testing requirements, changes in the expectations for data submission in marketing applications, and lengthening timelines. Addressing these criticisms will require the production-model culture to think beyond the narrow focus of bringing about greater reductions in review times.

For relatively mature technologies, improvements may require reassessment of requirements based on new information and gaps in knowledge with an appropriate benefit/risk assessment. For technologies that have fundamental similarities to these mature technologies but offer a substantial advance in safety and/or effectiveness, an unquestioned presumption of the applicability of data requirements for the mature technology is not appropriate. This can lead to an expenditure of time and resources conducting noninformative tests that ultimately do not provide a reasonable assurance of safety and effectiveness in the eyes of the FDA review team. Documentation of an appropriate benefit/risk assessment to identify the information needed to evaluate the device should help not only to minimize wasted steps, but also to avoid changes in the agreed-upon testing requirements during device development.

For highly innovative devices and clinical indications that do not have a historical basis for their regulatory and testing requirements, hoped-for improvements in the regulatory system will require a change in culture, not further refinement of the production culture.

THE UNITED STATES DEVICE REGULATORY SYSTEM AS AN INNOVATION MODEL

In contrast to the production-line culture, an innovation culture is fostered by an environment that permits disruption, puts people and ideas first, allows the whole system to be viewed through a new lens, and enables people—and therefore the organization—to grow and learn from mistakes.

At the heart of any culture are individual workers who adopt certain mindsets. The culture of an organization consists of the combination of the activities, values, and thinking of individual workers. The contrasting philosophies that give rise to the production culture and the innovation culture are summarized in the *Production Versus Innovation Cultures* sidebar.

CDRH is currently experimenting with ways to facilitate the development and evaluation of innovative medical devices in the United States, drawing from the culture and mindset of innovators. These efforts include: (1) publica-

PRODUCTION VERSUS INNOVATION CULTURES

Production Mindset

- Success is achieved when the process steps are complete.
- Change can only occur in increments.
- Failure is not allowed.

Innovation Mindset

- Success is achieved when the goals are met; this requires improvising solutions to problems.
- Change occurs through disruption.
- Failure brings about the necessary learning that leads to success.

tion of the draft Early Feasibility Study (EFS) Guidance Document (http://1.usa.gov/WHstqt), which utilizes benefit/risk principles to justify study initiation and permits further device development during the early clinical evaluation phase, and (2) the Innovation Pathway project (http://1.usa.gov/12s1KGk), which aims to reduce the time to market for innovative medical devices and to foster collaboration between the FDA and innovators.

EFS GUIDANCE

The EFS Guidance will provide a regulatory toolkit for sponsors and regulators to think in new ways about device development and the appropriate evidence needed to move from bench to clinical evaluation.

CDRH recognizes that for some new devices, exhaustive nonclinical testing would not likely provide the information needed to further device development. In these cases, early clinical use of the device in a limited number of subjects is needed to provide initial insights into clinical safety and device function, inform subsequent clinical and nonclinical testing, and/or improve device performance through iteration before finalizing the design.

As such, approval of an EFS IDE may be based on less nonclinical data than would be needed for a clinical study intended to support a marketing application, but must be supported by an appropriate benefit/risk analysis, including justification for the types and amount of data needed to support study initiation. The type of analysis needed is described in the EFS Guidance as the "Device Evaluation Strategy."

The Device Evaluation Strategy within the Report of Prior Investigations is intended to share the thinking behind the device development program with the FDA. The sponsor outlines the functions and features needed for the device to perform as intended, what can go wrong if the functions or features are not achieved, and what can be expected to happen to the device or patient if a failure occurs. Information used in the design of the device and prior nonclinical and clinical information from similar devices or intended uses are described to help identify gaps in the information needed to justify study initiation. The planned testing on the device to be used in the clinical study is presented, along with clinical protocol risk mitigation strategies that will be in place during the clinical study to help increase patient safety.

Although the Device Evaluation Strategy for an EFS should identify all known potential risks, it is recognized that there may be some unknown risks, particularly early in device development, and that some risks are more significant than others. An emphasis is placed on the basic safety (eg, biocompatibility) and on minimizing foreseeable risks that could be associated with a catastrophic failure of the device.

The Device Evaluation Strategy provides documentation that can be referenced and updated throughout the device development process. This method deviates from the usual approach of trying to fit existing device-specific guidance and voluntary standards (however limited in their applicability) to novel technology, resulting in sponsors prematurely completing all conceived testing (eg, on a nonfinalized device design for which modifications can be expected).

INNOVATION PATHWAY PROGRAM: SHORTENING TIME AND IMPROVING COLLABORATION

In 2011, a priority review program was launched for pioneering technologies that address unmet clinical needs and have the potential to revolutionize patient care or health care delivery. Called the Innovation Pathway, the program has two goals: (1) to shorten the time it takes for innovative medical devices to get from concept to market, and (2) to completely transform the relationship between innovators and the FDA. Designed by a team of FDA staff and managers working with the White House-sponsored Entrepreneurs in Residence program (http://1.usa.gov/WRFLq0), the Innovation Pathway program selected three projects from an End-Stage Renal Disease Innovation Challenge (http://1.usa.gov/10f0k0k) to test the new paradigm. Evaluation of the program is continuing, with the projects having completed the first phase of intensive interaction between the sponsor and CDRH called the Collaboration Phase.

The Collaboration Phase used a set of guiding principles (called the *Playbook*) that served to shape the culture and thinking of the innovators and FDA, a process that was facilitated by an independent case manager from outside the review divisions. Reviewers were encouraged to see them-

selves as being on the same team as the innovators; that is, working with sponsors who have developed promising new devices to address unmet clinical needs in the care of patients with end-stage renal disease. There was a day-long kick-off session that served to introduce members, understand the technology, and begin to construct a game plan for the Collaboration Phase. The teams set objectives for the interaction period, such as reaching agreement on the data needed to support the initiation of a clinical study or identifying the potential regulatory pathway toward marketing, and in each case voluntarily extended their collaboration in order to achieve their goals rather than "stopping the clock" at the suggested 120-day mark.

Both the FDA and innovators benefitted from the demands of this new program. Even though the FDA teams estimated that they devoted more than 25-fold the amount of interaction time for a typical presubmission, there was overall acceptance of the general principles and a belief that the program was worthwhile. For example, one FDA branch was particularly gratified by their interaction with professional societies, where they acted as partners in addressing the needs of patients with end-stage renal disease by providing the regulatory expertise to guide the project forward. Innovators felt that their participation in the Innovation Pathway and direct interaction with FDA staff enhanced the device development process.

This year, CDRH is continuing to use the Entrepreneurs in Residence program to tackle three new challenges within the innovation ecosystem for medical devices:

(1) Streamlining clinical trials: Finding ways to reduce the time and cost of clinical trials in support of FDA approval or clearance of medical devices.

(2) Streamlining the FDA approval-to-CMS coverage pathway: Finding ways to reduce the inefficiencies and delays in data collection to support FDA approval and CMS coverage.

(3) Striking the right balance between premarket and postmarket evidentiary requirements: Finding ways to allow efficient use of premarket studies to allow for timely approvals, with greater emphasis on capturing informative real-world data in postmarket studies.

After thoroughly investigating the challenges in each of these areas, the teams will pilot methods to test new concepts. For example, the team assigned to address premarket and postmarket balance is facilitating the design of a postapproval study that would allow manufactures to work together to answer questions related to the use of endovascular grafts to treat type B aortic dissections, using the Society for Vascular Surgery Vascular Quality Initiative registry. The premarket requirements to allow for modification of the thoracic endovascular graft labels to include the treatment of dissections would be relatively easy to meet. Postmarket, high-quality, real-world data would then be collected to address general clinical questions regarding the treatment of dissections (eg, the optimal length of coverage and timing of the intervention) and to provide information to further refine the labeling for individual devices postmarket.

SUMMARY AND CONCLUSIONS

The assessment of regulatory systems should consider the trade-off between having a wider selection of treatment choices and the availability of more evidence to support those choices. If the metric for success of a regulatory system is solely time to product approval, the FDA will appear to be deficient when comparisons are made to systems that have less strict regulatory requirements. Other systems may be associated with quicker approvals of some products, but these are achieved with less certainty that the product will be of benefit to patients. Recognizing problems inherent in the United States regulation of medical devices helps to drive improvements in our system.

The production model is a relatively reliable, efficient method of handling the vast quantities of regulatory applications reviewed by ODE, but further reforms are needed to improve performance. For innovative medical devices, new regulatory approaches are under development. In addition to meeting MDUFA performance goals, the application of benefit/risk principles throughout the regulatory process for both innovative and less novel devices is critical for the FDA to meet its public health mission. The value of the information requested by regulators must be weighed against the cost of capturing the information (eg, opportunity costs of resources utilized, time needed to complete testing, the possibility of noninformative test results, and delays in regulatory decision making) at different times during the device development process.

Regulatory system reform will involve a cultural shift, requiring education and training of review staff and sponsors, with the EFS efforts and Innovation Pathway serving as the proving ground. Advances realized through these projects should allow sponsors and review staff to successfully navigate the regulatory pathway for devices on the Innovative Pathway and those regulated under the production model, with the ultimate goals of promoting public health and enhancing patient safety and welfare. ■

Dorothy B. Abel is a Regulatory Review Scientist, Andrew Farb is a Medical Officer, and Megan Moynahan is the former Assistant Director for Technology and Innovation with the US FDA Center for Devices and Radiological Health in Silver Spring, Maryland. Ms. Abel may be reached at (301) 796-6366; dorothy.abel@fda.hhs.gov.