



## Post-Market Approval Surveillance

### A Call for a More Integrated and Comprehensive Approach

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The availability of new therapies over the past 2 decades has dramatically changed the practice of medicine. The introduction of medical devices has ushered in the era of minimally invasive procedures, thus fundamentally changing many surgical disciplines and creating new sub-specialties. Nowhere has the impact of new device technology been more dramatic than in the discipline of interventional cardiology. In addition to driving the growth of the medical device industry, device development has spawned entire new industries devoted to the coordination and administration of clinical trials. For a company to market a new high-risk device in the United States it must obtain approval from the Food and Drug Administration (FDA) based on the ability to demonstrate safety and effectiveness.<sup>1</sup> For a new interventional device like a drug-eluting stent, this is typically accomplished by performing large, multicentered, randomized controlled studies. These studies are performed by clinical investigators at research institutions on highly selected patients that may represent a small sector of the population for which the device is being developed. FDA approval is typically limited to the patient population studied, which is specifically outlined in the package labeling and instructions for use. Nevertheless, it is generally understood that after market release, devices are commonly used outside

the narrow confines of the pivotal study's selection criteria by operators with a wide spectrum of training and experience at institutions lacking the infrastructure or competency of the research institutions where the pivotal trials were performed. It is assumed that the benefits of device use demonstrated in the pivotal trials can be generalized to a wider patient population in the general clinical community. Whereas large resources have been devoted to the early development and clinical evaluation of new medical devices, few resources have been focused on post-market surveillance, which is the systematic evaluation of these therapies after FDA approval. 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. One focus of the symposium was the role of post-market surveillance.

#### The Current Landscape

Medical devices are regulated in the United States by the Center for Device and Radiologic Health (CDRH) of the Food and Drug Administration. In addition to its role in the evaluation of new devices, the FDA/CDRH charter includes the regulation of devices after approval. Currently, this function has been carried

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The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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This article is the result in part from Sessions at the Dartmouth Drug and Device Development Symposium (3DI) held at the Woodstock Inn, Woodstock, Vt, October 30 and 31, 2003.


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(*Circulation*. 2004;109:3073-3077.)

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*Circulation* is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000134694.78653.B6



out primarily by the Medical Device Reporting (MDR) program. Since 1984, medical device manufacturers and importers have been required to have processes in place to respond and report to the FDA any device-related deaths, serious injuries, or certain malfunctions.<sup>1</sup> Manufacturers become aware of these incidents primarily through the cooperation of clinicians and the device user facilities. Studies during the late 1980s by the General Accounting Office demonstrated that this process missed all but 1% of these events.<sup>2,3</sup> In response to these findings, Congress passed the Safe Medical Devices Act of 1990, which required user facilities to report device-related deaths directly to the FDA as well to the manufacturer. In addition, the user facility is required to notify the manufacturer of nonlethal events, including serious device-related injuries and malfunctions.<sup>4,5</sup> The FDA actively maintains a database, which summarizes all medical device reports it receives.

In addition to the medical device reporting (MDR) system, the FDA/CDRH has the power to mandate a more formal post-market surveillance program for certain devices, including permanent implants like pacemakers and stents or life-sustaining devices like left ventricular assist devices. These programs primarily focus on morbidity and mortality and the impact of a device failure. On device approval, the FDA notifies the manufacturer that it is subject to post-market surveillance. The manufacturer must submit to the FDA/CDRH a post-marketing surveillance program within 30 days after market launch.<sup>6</sup> The FDA then has 60 days to review the protocols and can require studies lasting as long as 36 months. Studies longer than 36 months require the manufacturer's agreement.<sup>7</sup>


Thus, the MDR system is the principal means by which the FDA monitors the safety and effectiveness of a device after approval. This system relies heavily on clinicians and the facilities where the devices are used (primarily hospitals, outpatient facilities, and nursing homes) to provide reliable information. Though the FDA processes more than 120 000 medical device reports annually, this system has many inherent flaws that severely limit its utility.<sup>8</sup> Reports are commonly cursory and neglect factors that might help identify specific problems. Physicians and facilities where devices are used have no incentive (and at times have disincentives) to take part in this system. For example, physicians encountering adverse events while performing off-label procedures may be reluctant to call undue attention to themselves for using a device in an unapproved manner. In addition, even when a physician or facility files a medical device report, there are few processes in place to assure data quality. Finally, the FDA has limited authority over physicians and hospitals. The net result is that MDR is of varying quality with significant and poorly characterized reporting biases.

In contra-distinction to individual practitioners and user facilities, manufacturers are directly under the jurisdiction of the FDA, which has considerable power to ensure compliance. In addition, manufacturers have long-term interests to determine the nature of adverse events and to identify,

characterize, and address any such problems in timely fashion. The FDA has considerable enforcement power including seizure, injunction, criminal prosecution, civil penalties, and recall authority to ensure rapid disclosure by companies.<sup>9</sup> This dynamic often limits a manufacturer's ability to screen reports and provides incentives to indiscriminately pass along every complaint in the form of a medical device report. Despite the considerable resources both industry and the FDA may devote to evaluating medical device reports, the sporadic nature of the reporting and variable quality of data make it difficult if not impossible to discern the magnitude of the problem under consideration.

Within the European Union, there is a similar requirement for manufacturers to report serious adverse incidents to the relevant regulatory authority in each member state.<sup>10</sup> These reports are now brought together in a centralized European database (EUDAMED). Efforts to standardize the reporting of serious adverse events and devices failures globally has been the focus of the Global Harmonisation Task Force, which represents the European Union, the United States, Canada, Australia, and Japan.<sup>11</sup> The United Kingdom arguably has the most developed user reporting system in Europe. In addition to reporting regulations, compliance is supported by the liaison officers regulated in every major hospital and primary care trust. Part of the role of the liaison officer is to make an initial assessment of the reported adverse incident and to encourage copious and high-quality reporting.<sup>12</sup>

The recent introduction of the Cypher drug-eluting stent by Cordis/Johnson and Johnson provides an illustration of deficiencies within the current system. The market launch of the Cypher stent was the culmination of a large development process that took nearly a decade, costing Cordis/Johnson & Johnson over \$100 million dollars. The clinical development process started with the First-In-Man Study, a small, 30-patient, single-center, single-arm study with angiographic follow-up. Angiographic evaluation at 6 months after stent deployment demonstrated 0% restenosis and ignited intense interest in the Cypher stent.<sup>13</sup> This was followed by the Randomized Study with the Sirolimus-Coated BxVelocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions (RAVEL) and Sirolimus-Eluting Stents versus Standard Stents in Patients with Stenosis in a Native Coronary Artery (SIRIUS) multi-center trials which randomly assigned patients to receive Cypher drug-eluting stents (653 patients combined) or bare metal stents of the same design (643 patients combined). The results of these studies demonstrated a dramatic reduction in target vessel failure (death from cardiac causes, Q-wave or non-Q-wave myocardial infarction, or repeat revascularization of the target vessel) of 68% (RAVEL) and 83% (SIRIUS) in stable patients undergoing single vessel percutaneous coronary intervention of relatively uncomplicated target lesions. Combining the RAVEL and SIRIUS studies' subacute stent thrombosis rates shows thrombosis in only 1 of 653 Cypher stent patients (0.15%) and in 1 of the 643 control



patients (0.16%). Similarly, late thrombosis was observed in 2 of Cypher stent (0.31%) and 3 of the control (0.47%) patients.<sup>14,15</sup> These studies were too small and lacked the statistical power to discern differences in subacute and/or late thrombosis rates between test and control groups. Based on the result of the First-In-Man, RAVEL, and SIRIUS studies (a total of 683 patients receiving drug-eluting stents), the FDA approved the Cypher stent for “patients with symptomatic ischemia due to discrete de novo lesions of length  $\leq 30$  mm in native coronary arteries with reference vessel diameter of  $\geq 2.5$  mm to  $\leq 3.5$  mm.”<sup>16</sup>

The impact of these data on the interventional cardiology community is difficult to underestimate. Since the introduction of coronary angioplasty in the late 1970s, restenosis has continued to limit the overall utility of percutaneous coronary revascularization procedures. Efforts directed at solving restenosis received intense focus by both the clinical and medical device communities. During this time, well over 100 different restenosis reduction strategies have been evaluated in  $>1000$  clinical studies without identifying a practical approach with durable efficacy. The introduction of the Cypher stent provided a practical strategy with early data supporting efficacy for near elimination of restenosis. The strength of these data coupled with the Cordis/Johnson & Johnson marketing resources and expertise resulted in an explosive market launch for the Cypher stent. In the first 5 months after the US market launch, Cordis/Johnson & Johnson reported distributing 260 000 stents, representing more than \$725 million dollars in sales.<sup>17</sup> These facts are even more impressive when one considers that Cypher stent adoption was limited by product availability.

After the market release, Cordis/Johnson & Johnson and the FDA via the MDR system began to receive reports of subacute stent thrombosis (SAT) as well as possible hypersensitivity reactions. Specifically, the FDA received 290 reports of SAT, with subsequent death in more than 60 of these cases. This represented an increase in the number of reports received by the FDA (verification required), although the inherent limitations of the MDR system made it impossible to discern if these reports represented an increased risk of SAT for the Cypher stent compared with bare metal stents, or rather an increased frequency of reporting of these events because of the high profile of this product. Concern regarding the implication of these cases prompted the FDA to issue a Public Health Notification on October 29, 2003.<sup>17</sup> The early impact of the notification was to cause much concern on the part of patients and clinicians, as well as solicitation of lawsuits by the personal injury bar. The long-term impact on Cypher stent usage, however, seems to have been minimal. Despite much focus on this issue in the ensuing 5 months, a better understanding of the impact of drug-eluting technology on SAT is lacking. An understanding of the factors that lead to SAT would provide the clinical community with the opportunity to reduce the rate of this serious complication. This example underscores the current need for more effective

monitoring after the introduction of devices such as the Cypher stent.

## Proposed Solutions

### Pre-Market and Post-Market Approval


The regulatory process is split into 2 distinct phases, pre-market and post-market approval. For a new high-risk device, the pre-market approval phase is focused primarily on the demonstration of safety and efficacy through pivotal clinical trials. The post-market approval phase is focused primarily on ensuring adherence to good manufacturing practices, which include mechanisms for identifying device failures.<sup>4–6</sup> These 2 phases are typically treated as 2 distinct stages by industry, the FDA, clinicians, and the public. Within the cardiovascular division at CDRH at FDA, the pre-market and post-market approval staffs are distinct and separate. Though easy to define, this separation is artificial and leads to a dynamic that has the tendency to ignore issues of safety and efficacy which may be encountered after approval, specifically with the integration of a new technology into the clinical armamentarium. A regulatory approach, which treats the device development process as a continuum beginning with First-In-Man extending through market launch to when use is routine and well understood, would provide a more realistic framework to address issues of safety and efficacy.

An example of such an integrated approach can be found in the regulatory treatment of agents to treat HIV/AIDS. Protease inhibitors have become a cornerstone of treatment for patients with HIV/AIDS. Approval was based on early small trials that demonstrated positive effects on surrogate markers and were supplemented by large, registry-like, single-arm trials to better document safety. The full picture of clinical effectiveness was not demonstrated until randomized trials were completed in the post-marketing period.<sup>18</sup> Large registries will have a greater ability to more accurately characterize rare severe adverse events than is afforded by relatively small randomized trials.

An approach in which a comprehensive post-market surveillance strategy is established as part of the approval dialogue between the FDA and the companies that market medical products may allow for a more streamlined approval process and could provide the regulatory authorities, clinicians, and patients with more relevant data to guide use of new devices as they are introduced into the marketplace. Furthermore, such a forward-looking strategy would also allow for utilization of the clinical trial machinery established for the pivotal trial(s).

### Industry Incentive

The current dynamic that separates pre-market and post-market phases often provides disincentives to a company (and its competitors) to provide the large resources required for comprehensive post-market study programs. This is clearly the case when the clinical community spontaneously expands the use of a device beyond settings specified in the label. For



example, drug-eluting stents are being routinely used in the setting of acute infarct angioplasty. Although it is cogent to believe that this strategy will reduce in-stent restenosis without significantly increasing the risk of thrombosis (acute, subacute, or delayed), the data to support such practices are scant. If market adoption continues, there will be little incentive for the company to study these issues more thoroughly. The impact of drug-eluting stent technology on in-stent restenosis as well as on SAT rates could be discerned by data obtained from a large, robust, post-market surveillance program. The ability to use such data to expand the labeled indications for a device would provide an important incentive for a company to fund these programs.

### Claims-Based Data

An understanding of how a new device is utilized, as well as its impact on significant end points such as re-hospitalization and death, can be gleaned from claims databases. The most comprehensive claims database within the United States is maintained by Medicare and has the potential to provide a comprehensive understanding of the impact of a new technology on the over-65 age group. Availability of these data will allow for examination of death, re-hospitalization for unstable angina, myocardial infarction, or stroke after a procedure such as percutaneous coronary revascularization. One of the strengths of this approach is that it allows for sampling of the entire spectrum of clinical sites, including centers not typically involved in clinical studies. It is clearly in the interest of payors to help facilitate a better understanding of the implementation of new technology.

Outside the United States, differences in the healthcare delivery systems have facilitated availability of longitudinal patient data. For example, the United Kingdom General Practice Research Database (GPRD) is already used by the FDA for pharmaceutical investigation and has the potential to be used in the future to assist in the post-marketing surveillance of medical devices.<sup>19</sup>

We believe that claims-based databases are underutilized resources and need to be incorporated into the monitoring of new devices.

### Device-Specific Registries

As outlined above, the use of a device after approval and release for general use typically differs from the conditions under which the pivotal studies were performed. Therefore, it is important to establish ongoing registries that capture usage from the entire “real world” spectrum to include experienced and inexperienced operators, high- and low-volume centers, comorbid and otherwise healthy patients, and off-label use.

One approach is to include within the packaging a simple clinical research form to be filled out by the operator at the time of implantation. These data could then be entered into a prospective database. Follow-up for patients could be obtained by monitoring insurance claims. To avoid confidentiality issues, encryption technology exists to allow for follow-up while maintaining patient confidentiality. The

strength of this approach is that it eliminates some of the selection biases inherent with the use of existing registries, which tend to favor higher volume, more expert institutions and operators.

Another approach is to establish a group of study centers that obtain data on all patients who receive treatment with a specific device. In assembling such a study group, it is important to ensure that a broad spectrum of centers is included. Furthermore, when possible, an effort to standardize the data acquired will be beneficial when comparing outcomes to other interventions. A unified set of FDA-authored guidelines setting standards for post-approval surveillance studies would be extremely useful in setting the bar for the quality of data expected and required of institutions wishing to participate in this process. These guidelines might come in the form of an overall guidance document and could be used as the basis for a certification process, to verify that an institution’s infrastructure and ability to gather data are acceptable. Standards codified in this manner would impress on trial sites that their responsibilities do not end with the pre-market phase, but extend into the post-market period as well.

Likewise, this “good practices” document would demonstrate to manufacturers how to perform post-approval studies, so that industry and clinical trial sites can provide the FDA with quality data capable of supporting an expanded indication as well as demonstrating safety.

### Societies/Database Sharing

Often overlooked are existing databases from large single institutions, eg, Cardiovascular Research Foundation, the Mayo Clinic Foundation, Duke University, and Cleveland Clinic Foundation, and multicenter data banks, eg, American College of Cardiology, American Heart Association, and National Heart, Lung and Blood Institute. Pooling data from these existing data banks has the potential to provide the FDA and the clinical community with high quality data with which to evaluate safety and efficacy issues in the post-market phase.

For cardiovascular interventional devices, there are a number of large databases that exist in European member states and that can be a valuable source of information. There is currently a move within the European Union to attempt to integrate some of these databases and registries. Longitudinal patient record systems may also yield valuable data. For example, the United Kingdom General Practice Research Database is already used by the FDA for pharmaceutical investigation and has the potential to be of use in the future to assist the post-marketing surveillance of medical devices.<sup>20</sup>

A recent example of this approach is the examination of transmyocardial revascularization (TMR) using the Society of Thoracic Surgeons National Cardiac Database (STS Database).<sup>21,22</sup> TMR was approved by the FDA for “the treatment of stable patients with angina ([Canadian Cardiovascular Society] Class 4) refractory to medical treatment and secondary to objectively demonstrated coronary artery atherosclerosis and with a region of the myocardium with reversible

ischemia not amenable to direct coronary revascularization.<sup>22</sup> Approval was based primarily on a randomized study comparing TMR to medical therapy in the treatment of stable angina patients that demonstrated a reduction in angina, anginal medications, cardiac hospitalization, and exercise performance. There was no significant impact on mortality at 12 months. Concern about the off-label use of TMR led to review of the STS Database. The STS Database collects data from approximately two-thirds of all US cardiothoracic hospitals. The data showed that over the length of the study, the number of sites performing TMR grew rapidly, from 33 in 1998 to 131 in 2001. The vast majority (79%) of the 3136 patients who received TMR were treated off-label (TMR + coronary artery bypass grafting). In addition, a significant proportion of patients were selected for TMR with unstable symptoms (myocardial infarction within 21 days of procedure, unstable angina). These patients had mortality rates nearly twice those of more clinically stable subjects.

Further utilization of existing databases to evaluate safety and efficacy of recently approved devices may provide a means to monitor the utility of both on- and off-label use.

### Conclusions

This article outlines the regulatory challenges encountered after a new device is introduced into the marketplace. The current MDR system has major deficiencies and provides inconsistent data. New approaches are required to provide the FDA, clinicians, and the industry the appropriate data with which to monitor and understand new technologies as they are integrated into the clinical armamentarium.

First and perhaps most important is the recognition that the post-market approval phase is part of a continuum starting with first clinical use and extending through the pivotal trial(s) and market launch. As such, a post-market surveillance program needs to provide the means for monitoring the safety and efficacy of a specific device beyond the restrictions of the early registration trials as it is released to the general clinical community. When designing a post-market surveillance program, the following approaches should be considered: Establishment of a multicenter registry, evaluation of existing data banks, and evaluation of claims data banks. Because many issues arise with market launch, to quickly identify and respond to problems, it is imperative to have a post-market surveillance program in place at the time of market launch.

Building a collaboration among regulators at the FDA, clinician investigators, and industry is essential for successful implementation of a post-market surveillance program. These programs have the potential to provide high quality data that reflect the real world use of the device and allow for the detection of low frequency serious adverse events. In addition to its monitoring function, the availability of these data can provide justification for expanded indications for use. Ultimately, validation of such a system may allow for earlier device approval. Both earlier device approval and a more efficient mechanism for expanding indications for use will

provide important incentives for companies to invest the resources required for a comprehensive post-marketing program.

Recent post-market issues involving the Cypher stent highlight the need for improved post-market surveillance programs. Implementation of a comprehensive post-market surveillance program has the potential to bring medical devices to the market earlier while providing clinically appropriate data to facilitate a higher standard of care for our patients.

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