

# Cardiovascular Device Development: Drug-Eluting Stents and Implantable Devices for the Treatment of Heart Failure—the View from the Circulatory System Advisory Panel

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The development of sirolimus and paclitaxel-eluting stent delivery systems proved successful in reducing restenosis rates to single digit levels compared to bare metal stents, although the long-term safety of the latter devices was not assessed in these premarket applications. Implantable devices for the treatment of patients with advanced congestive heart failure improved short-term measures of circulatory function but underscored the role of properly conducted randomized controlled clinical trials. All of these examples highlight the critical role of valid scientific evidence in the regulatory process for cardiovascular device development.

*Keywords:* device development, regulations, advisory panel

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## INTRODUCTION

The past 5 years at the US Food and Drug Administration (FDA) have been witness to a remarkable number of “breakthrough” technologies for the treatment of patients with cardiovascular disease. The arrival of drug-eluting stent (DES) premarket applications (PMA) at the Agency was much anticipated given the promise of this modality noted in preclinical studies. The promise of transpharmacologic treatment modalities for patients with congestive heart failure represented an analogous quantum leap in the treatment of these desperately ill patients. The following represents a broad (and brief) overview of the many deliberations of the Circulatory System Advisory Panel in these two areas.

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## DRUG-ELUTING STENTS

### Sirolimus

The recurrent cycle of hope followed by disappointment, which characterized the search for a means of minimizing the risk of restenosis following percutaneous coronary intervention (PCI) and which lasted for over 2 decades, was finally broken on October 22, 2002. At this session, Cordis Corporation presented a PMA in support of the sirolimus-eluting CYPHER stent to the Advisory Panel. Building on the strength and success of a strong preclinical experience followed by encouraging phase I safety data, the results of the pivotal clinical trial (SIRIUS) clearly established superior safety (MACE [major adverse clinical events]) and efficacy (TVF [target vessel failure]) at 9 months with the sirolimus-eluting stent when compared with the identical bare metal stent platform. Although a number of methodologic and practical clinical concerns were adduced, the panel voted unanimously for approval of the PMA with, however, a number of important conditions. The latter reflected the panel’s concerns with respect to the data supporting a wider range of lengths and

dimensions than were actually available and the requirement for prolonged, ie, 5 years, follow-up for patients in the PMA. The former raises important questions regarding "off-label" use of the product (eg, stent dimensions <2.5 or >3.5 mm; stent length >30 or <15 mm), while the latter speaks to questions related to both efficacy (maintenance of treatment effect) and safety (delayed adverse events). Additionally, the detection of infrequent, albeit serious, adverse events was recognized and provided the basis for recommendations for expanded postmarket surveillance efforts to more precisely quantify this risk.

### Paclitaxel

On November 20, 2003, Boston Scientific Corporation (BSC) presented a PMA in support of a paclitaxel-eluting stent. Also based on a strong preclinical effort and phase I safety data, the BSC PMA was a compendium of smaller, randomized clinical trials in addition to the pivotal TAXUS-4 trial. The latter established superior safety (MACE) and efficacy (TVR) at 9 months with a paclitaxel-eluting stent compared with an identical bare metal stent platform without drug or polymer vehicle. Once again, the panel voted unanimously for approval with, once again, a number of conditions. These conditions reflected concerns regarding potential drug-drug interactions, DES stent-stent interactions, and the appropriate length of antiplatelet/antithrombotic therapy. Notably, the sponsor had already proposed post-marketing studies for the pivotal trial patients (up to 5 years) as well as "real world" registries examining product use unconstrained by adherence to the clinical protocol.

Table 1 summarizes the treatment effects of sirolimus- and paclitaxel-eluting stents (DES) compared with bare metal stents (BMS).

### *Lessons learned and challenges for future evaluation of DES*

The benefits of DES technology are but one side of the coin. The same inhibition of the restenotic process carries with it the risk of incomplete/inadequate endothelialization and, therefore, the risk of thrombosis. Considerations such as dose, dose rate, lesion characteristics, clinical presentation, and antithrombotic therapy are further confounders not rigorously addressed in the "pivotal" trials. Continued open-access registries, a condition for approval of both the above PMAs, allows for more precise quantification of the risk of adverse events. However, given the constraint that the conduct of these additional procedures mirror the conduct of the parent RCT, few "real-world" outcome data are expected. Thus,

registries of real-world use have also been recommended to more fully capture the true therapeutic potential (as well as hazard) of DES.

## DEVICES FOR THE TREATMENT OF HEART FAILURE

### Cardiac resynchronization therapy

Despite remarkable advances in the pharmacologic treatment of patients with severe heart failure, persistently high rates of mortality and/or repeat hospitalization have stimulated the need for additional therapies. It is on this background ("best" medical therapy) that mechanical approaches to the treatment of patients with chronic, congestive heart failure (CHF) were evaluated. As discussed by Dr. Maisel, implantable devices aimed at reducing the incidence of arrhythmia-mediated death in patients with depressed left ventricular function have proved to be remarkably effective. The competing cause of mortality in such patients is continued deterioration in circulatory performance. Long recognized as deleterious in patients with compromised ventricular function, univentricular (RV) pacing was modified to include simultaneous LV pacing. Improvements in incoordinate cardiac contraction, increases in stroke volume and cardiac output and normalization of a previously prolonged QRS complex were reported in various case series. Whether such acute improvements translated into meaningful clinical improvements, and in whom, became the subject of an intense investigational program for several device manufacturers. Initial clinical trials included patients with NYHA Class II-IV CHF and focused on functional outcomes. However, it was recognized that the more severely compromised patients, eg, NYHA Class IV, were more likely to die or progress to cardiac transplantation by 1 year, and, therefore, these functional end points were evaluated at 6 months.

On July 10, 2001, both Guidant and Medtronic presented data in support of their respective PMAs for cardiac resynchronization therapy (CRT) devices. It is notable that all patients in the Guidant protocol were candidates for internal cardiac defibrillator (ICD) implantation, while this was not true for the patients in the Medtronic PMA. Differences in study design and patient populations preclude comparison of these data sets. While the composite primary end point at 6 months (all-cause mortality, hospitalization, the occurrence of ventricular tachyarrhythmias) was not significantly different between the 2 arms of the Guidant study, the coprimary end points in the Medtronic study (6-minute walk, quality-of-life measure, and NYHA functional class) were each significantly different between treat-

ment and control arms at 6 months. Accordingly, the panel voted for nonapproval of the Guidant PMA and approval of the Medtronic PMA. However, most panel members thought that 6 months was an insufficient period of time to meaningfully assess efficacy and reliability. Additionally, the strong placebo effect noted in the control arm of the Medtronic study emphasized the need for “harder,” more objective end points in such non-mortality trials.

A PMA submission by Medtronic on March 5, 2002, included patients with an indication for an ICD who also were functional class NYHA Class III/IV (n = 554). In this randomized controlled study, only 2 of the above-mentioned coprimary end points (quality of life and NYHA class) were found to significantly differ between groups at 6 months. There was considerable discussion of these data, with an emphasis on the study design, device efficacy, and safety. Initially, the panel was deadlocked and an initial motion for nonapproval was rejected as a result of the chair’s tie-breaking vote. Subsequent detailed discussion among panelists led, ultimately, to a vote for approval with conditions, although again as the result of a tie-breaking vote by the chair. The conditions recommended reflected the panel’s ongoing concerns with respect to appropriate measures of efficacy of device therapy for patients with CHF. Thus, an analysis of mortality at 12 months in the IDE population and longer term, ie, 3 years, data in the form of a registry for mortality and lead performance in a larger sample were recommended.

As discussed, the aforementioned PMAs and their respective pivotal trials employed primary end points and outcomes that were somewhat subjective and less than “hard.” The PMA submitted by Guidant Corp on July 28, 2004, represented the first application for CRT seeking approval for a reduction in the risk of all-cause hospitalization or all-cause mortality. With over 1500 patients with NYHA Class III/IV CHF enrolled, the

DSMB recommended to the steering committee that enrollment be stopped when the target number of primary end point events had been reached. The PMA was based on the outcomes in patients receiving CRT and ICD therapy compared with outcomes in patients receiving optimal pharmacologic therapy (OPT). This pairwise comparison differs from the analysis in the parent COMPANION trial whose results were published in the *New England Journal of Medicine*.<sup>1</sup> The PMA reported a statistically significant reduction (hazard ratio, 0.80; 95% confidence interval, 0.68–0.95) in the risk of all-cause mortality or all-cause hospitalization in the patients assigned to the CRT and ICD arms. Due to the absence of either CRT or ICD in the control population, it is impossible to attribute the treatment effect to either device, only to their conjoined effect. The panel voted unanimously to approve this PMA with, however, several conditions. The latter reflected concerns over the definition and adjudication of all-cause hospitalization, differential withdrawal of patients in the OPT arm and small differences in longer term (>1 year) mortality.

#### Left ventricular assist device (LVAD)

Despite these remarkable advances, a significant fraction of patients with CHF will progress to the point where the only viable option for reduction in the risk of dying is cardiac transplantation. The well-known shortage of donor organs is an even larger problem, and thus, until recently, many patients succumbed to either progressive cardiac or multiorgan failure while awaiting a transplant. LVAD have been considered a powerful, albeit temporary, stabilizing treatment modality for end-stage patients awaiting heart transplantation. Thus, the PMA discussed on March 4, 2002, from Thoratec was eagerly awaited. Expanding beyond the extant indication for use of LVAD as a bridge to transplantation, the unique feature of this PMA was its proposed indication for “destination therapy” or therapy until the end of life. The hypothesis tested was whether survival was improved in the LVAD treatment arm compared with patients receiving optimum medical therapy. Although the parent trial (REMATCH) results from which this data set was derived were published in the *New England Journal of Medicine*,<sup>2</sup> detailed deliberations by the panel, sponsor, and Agency centered on the clinical significance of the demonstrated benefit on survival in the LVAD arm compared with control arm (23% vs. 2%, respectively) at 2 years. This survival benefit needed to be viewed in the context of the small numbers of evaluable patients at 2 years, a significant increase in LVAD-associated complications (sepsis, neurologic events) and uncertain differences in quality-of-life metrics. Nevertheless,

**Table 1.** Treatment effects of sirolimus- and paclitaxel-eluting stents (DES) compared with bare metal stents (BMS).

End point	DES	BMS
Sirolimus		
TVF	8.6%	21%
MACE	7.1%	18.9%
Paclitaxel		
TVR	4.7%	12.0%
MACE	8.5%	15.0%

TV, target vessel failure; TVR, target vessel revascularization; MACE, major adverse clinical event.

the panel voted 8-2 for approval with conditions for approval reflecting approaches to further resolving these concerns.

*Lessons learned and challenges for future evaluation of the use of implantable devices for the treatment of patients with CHF*

The increased spectrum of disease complexity and severity, the ever-expanding potential capabilities of improvements in implantable devices, and the dynamic background of “optimum medical therapy” render scientifically sound, timely, and clinically relevant evaluation of device safety and efficacy a most difficult task. Recalling that device manufacturers must provide *valid scientific evidence* that their device is safe and effective *when used as intended*, it is clear that the current evaluation process must not only retain its intellectual rigor but also its relevance and responsiveness. As the intended populations are characterized by increasing likelihood of death or serious morbidity, questions regarding the location of the fulcrum of clinical “equipoise,” the ethics

of adherence to the classic randomized trial design, the difficulties of blinding physicians and operators (to implantable devices), and the use of placebo versus best medical treatment control arms bring enormous pressure to bear on the evaluation process. Innovative (but clinically relevant) trial design, appropriate end points, and validated metrics for their determination and the necessity for systematic assessment of real-world outcomes, particularly with respect to safety and reliability, will be necessary (but not sufficient) elements of the evaluation process.

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