FDA INSIGHTS

2008 FDA Guidelines for DES

The how and why of FDA oversight of drug-eluting stents.

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Congress tasks the FDA's Center for Devices and Radiological Health (CDRH) with ensuring that new medical devices demonstrate a reasonable assurance of safety and effectiveness before they are approved for commercial distribution in the US. The CDRH also monitors the performance of approved medical devices to assess their continuing risk/benefit profile.

In both clinical trials and practice, drug-eluting stents (DES) have considerably reduced the rates of restenosis and repeat revascularization compared with balloon angioplasty and conventional bare-metal stents (BMS). Since their initial approval in 2003, DES have emerged as the predominant catheter-based treatment for patients with obstructive coronary atherosclerosis in the US. During the last 2 years, new questions about DES safety have been raised, which prompted a comprehensive assessment of the FDA's review process for these important devices. The FDA's current thinking on the regulation of DES has been recently published in the draft *Guidance for Industry Coronary Drug-Eluting Stents—Nonclinical and Clinical Studies*.[1] This article will summarize DES regulatory history and discuss key elements of the FDA review of new DES.

HOW DES ARE REGULATED BY FDA

DES are combination products consisting of a stent onto which a drug-containing carrier (typically a polymer) is applied. Accordingly, DES applications are assigned to the CDRH for lead review with important consultation provided by the Center for Drug Evaluation and Research (CDER). FDA reviewers examine all individual DES components (delivery system, stent, polymer, and drug) as well as the complete finished product, including engineering, toxicology, biocompatibility, pharmacokinetic, and manufacturing aspects.

Because of their use in invasive coronary procedures, DES are regulated as class III (highest risk) devices. An approved Investigational Device Exemption (IDE) application—containing a detailed device description, proposed indications for use, preclinical and previous clinical experience, a summary of the manufacturing process, and the proposed clinical protocol—is required to conduct clinical studies of a new DES in the US. Approval of a Premarket Approval Application (PMA) is needed prior to marketing. PMA approval of a DES is based on valid scientific evidence that demonstrates that the device provides a reasonable assurance of safety and effectiveness under its conditions of use (its intended use).

BRIEF REGULATORY HISTORY OF THE DES APPROVED FOR USE IN THE US

The first two FDA-approved DES were the Cypher sirolimus-eluting coronary stent (Cordis Corporation, Warren, NJ; PMA approved April 24, 2003) and the Taxus Express2 paclitaxel-eluting coronary stent (Boston Scientific Corporation, Natick, MA; PMA approved March 4, 2004). In the pivotal clinical trials, both DES were associated with significant reductions in repeat revascularization (target lesion and target vessel revascularization [TLR and TVR]) rates compared with control BMS.[2] It is important to note that the randomized trials submitted for PMA approval enrolled patients with stable coronary disease and non-complex lesions.

Concerns about DES thrombosis, especially occurring late after implantation, emerged in 2006. Although the total number of reported cases was relatively small, these events raised an important safety signal based on the widespread use of DES (>80% of PCI procedures in the US) and the association of stent thrombosis with acute myocardial infarction (MI) or death. Presentations, publications, and FDA-required postapproval registry studies showed that DES use in complex lesions beyond the approved indications (eg, bifurcations, lesions requiring overlapping stents, or acute MI lesions), and in patients with multivessel stenting, renal dysfunction, and diabetes was associated with increased rates of stent thrombosis. In addition, premature discontinuation of antiplatelet therapy (APT) was identi-

fied as an independent risk factor for DES thrombosis. DES thrombosis concerns led the FDA to convene a meeting of its Circulatory System Devices Advisory Panel on December 7 and 8, 2006, to publicly review all available data on DES thrombosis and to address questions regarding the appropriate duration of APT. The notable conclusions from this panel meeting are available at http://www.fda.gov/cdrh/news/010407.html.

Data presented at and after the Advisory Panel meeting prompted the FDA to reappraise its review process that led to the approval of the first two DES, integrate lessons learned in the ongoing reviews of two DES with trials initiated before the Panel meeting (the Endeavor zotarolimus-eluting coronary stent, Medtronic Inc., Minneapolis, MN, PMA approved February 1, 2008; and the Xience V/Promus everolimus-eluting coronary stent, Abbott Vascular, Santa Clara, CA/Boston Scientific Corporation, PMA approved July 2, 2008)[3] and formulate FDA guidance for subsequent generations of DES. Furthermore, the DES thrombosis issue underscored the importance of continuous postmarket surveillance to ensure the continued safety of medical products after their approval for commercialization.

CURRENT FDA RECOMMENDATIONS FOR DES APPLICATIONS

Preclinical Overview

The DES Guidance (to be finalized by late 2008 or early 2009) contains a comprehensive description of the preclinical bench and experimental animal studies to be submitted in a PMA submission to fully characterize the drug-device combination product, including pharmacology and toxicology of the eluted drug, coating evaluation, drug release kinetics, and biocompatibility. Coronary artery DES implants in small and large animal models (eg, porcine coronary arteries) provide an evaluation of stent endothelialization, thrombus deposition, inflammation, arterial injury, and arterial remodeling. Because the mechanism of neointimal growth inhibition by a DES often involves a delay in arterial healing, long-term animal studies are recommended to confirm that unresolved pathologic findings observed earlier have been resolved (ie, complete healing). Studies of stents with drug dosages in multiples of the intended clinical dose (which expose the arterial wall to an overdose of eluted drug) and overlapping stents (a common technique in clinical practice) provide evidence of an acceptable safety margin. Overall, the major focus of preclinical in vivo studies is to demonstrate an acceptable level of safety so that clinical trials in humans may proceed.

Pivotal IDE Study Design

Prior to submission of a pivotal IDE study, it is often useful to obtain initial human data in feasibility or first-in-man (FIM) studies. FIM studies, in combination with a preclinical characterization of the new DES, support FDA approval to commence pivotal trials. The essential elements of the IDE protocol are presented in Table 1.

A randomized controlled trial (RCT) is the most appropriate pivotal study design for a DES that utilizes a completely new stent design, a new molecular entity (NME, a drug that contains an active moiety that has not been approved by FDA in any other application), and/or a stent with unique elution kinetics. A single-arm clinical study that utilizes a historical control may be acceptable for an iteration of an approved DES or expanded indication in a particular lesion subset or clinical setting. For a new DES that has differences from an approved device but is not completely novel, either an RCT or a single-arm study may be considered depending on whether the modifications are likely to have an impact on device effectiveness and/or patient safety.

The selection of the most appropriate pivotal trial design depends on the proposed indication for the use and the primary endpoint for comparison (eg, angiographic measure, composite clinical outcome or individual clinical event [eg, TLR]). A study designed to show superiority of a new DES to either an approved BMS or an approved DES is acceptable. If a superiority study is chosen, the investigational DES should be superior to the control stent by a margin considered to be clinically significant. Alternatively, a noninferiority (or equivalence) study can be proposed: (1) if it is not considered feasible to enroll patients in a superiority study that uses a BMS as a control or, (2) the objective of the trial is to show that the new DES is noninferior to an approved DES (active control). However, there are two issues that should be considered in the design of a noninferiority RCT:

- Selection of the noninferiority margin is a clinical judgment based on available previous studies and expected performance. The margin should be sufficiently small such that the investigational DES can still be considered to be clinically noninferior to the control.
- Serial noninferiority trials are subject to outcome drift, in which each subsequent DES is deemed statistically noninferior than its immediate predecessor, raising the possibility that after several trials, a later-generation DES could be no better or even inferior to the original control treatment (ie, a BMS).

Pivotal Study Endpoints

As clinical trial experience with DES has developed, study endpoints have been refined to reflect clinical endpoints that are most relevant to the studied device and treated vessel. For trials of new DES, the FDA recommends a device-oriented primary endpoint referred to as target

TABLE 1. ELEMENTS OF AN IDE PROTOCOL

- Statement of the intended use*
- Study hypothesis(es)
- Primary and secondary study endpoints for both safety and effectiveness
- Criterion for study success (ie, which hypotheses must be met for the study to be declared a success)
- Allocation of type I error (alpha) for primary and secondary hypotheses
- Plan for assessing safety in which all adverse events are identified and analyzed
- Plan for assessing safety and effectiveness on the basis of an intent-to-treat population as well as an evaluable population
- Study design with inclusion/exclusion criteria
- Case report forms
- Statistical analysis plan
- Risk/benefit analysis
- Informed consent document
- Data and Safety Monitoring Board (DSMB) charter
- Balance of premarket and postapproval data development
- Labeling that accurately presents any previously collected study data

**The intended use statement describes the lesion types (eg, de novo coronary lesion), the target population (eg, stable angina or acute coronary syndrome), anatomical sites of application of the DES (eg, native coronary arteries, left main lesions, bifurcation lesions, or bypass grafts), range of coronary lesion lengths and vessel diameters, and expected outcomes (eg, improving myocardial blood flow).*

lesion failure (TLF), which is a hierarchical composite of cardiac death, target vessel MI, and TLR. Formal null and alternative hypotheses should be prespecified in the protocol, and the primary endpoint should be assessed 12 months after DES implantation. At the time of PMA submission, 12-month clinical outcomes should be supplemented with 18- to 24-month follow-up data on a sufficient number of patients to assess any safety signals that might emerge after thienopyridine discontinuation. In addition, it is recommended that study subjects continued to be followed through 5 years after DES implantation.

Important secondary endpoints include the rates of the individual clinical components of TLF (cardiac death, target lesion MI, and TLR), TVR, target vessel failure (composite of cardiac death, MI, and TVR), all death, and acute procedural outcomes such as stent deliverability, deployment, and stenosis reduction. Secondary endpoints may be presented descriptively without formal hypothesis testing and, therefore, not leading to additional claims in labeling.

Imaging Endpoints

Angiographic follow-up studies are useful to assess local biologic responses such as in-stent neointimal proliferation (percent stent diameter stenosis and late lumen loss) and binary restenosis rates. Intravascular ultrasound evaluates stent volume obstruction by neointimal tissue and stent strut malapposition to the underlying arterial wall. Angiographic late lumen loss and percent diameter stenosis have been proposed as surrogate markers for the need for repeat revascularization. However, protocol-required follow-up angiography can confound TLR rates as a result of the oculostenotic reflex. Therefore, when protocol-required follow-up imaging studies are indicated, they should be performed after the time point of the evaluation of the primary clinical composite endpoint (ie, subsequent to the 12-month TLF assessment). Alternatively, protocol-required follow-up angiography may be performed in a separate cohort of patients outside of the pivotal DES trial. Late lumen loss or percent diameter stenosis may be considered as a primary effectiveness endpoint for iterative changes to an approved DES.

Assessing DES Thrombosis and APT

Stent thrombosis is a critical element of the safety profile of all coronary stents. With the emergence of DES thrombosis concerns, it became apparent that definitions of stent thrombosis varied across clinical study protocols, resulting in limitations in comparing thrombosis rates. Although other stent thrombosis definitions may be proposed, the FDA considers the Academic Research Consortium stent thrombosis definitions, which are based on the timing of the event and levels of supportive clinical data, to be acceptable for use in DES trials.[4]

Although premature discontinuation of dual APT is clearly associated with an increased risk of DES thrombosis, the optimal duration of continued thienopyridine use remains undefined. For new DES clinical studies, the FDA recommends that the following aspects of APT be addressed:

•The profile of patient compliance with recommended APT

•How often dual APT is being extended beyond the recommended duration

•The frequency and duration of APT interruption and clinical events associated with interruption

•The frequency of deferral of invasive or surgical procedures because of the need for continued APT

•The rate of significant bleeding complications associated with APT

ENSURING DES SAFETY: A CONTINUUM OF PRE-AND POSTAPPROVAL EVALUATION

Long-term follow-up of patients enrolled in the RCTs of the approved DES have demonstrated sustained effectiveness, defined as a reduced rate of repeat revascularization procedures compared to BMS. Cardiac death, MI, and stent thrombosis are considered to be safety endpoints. In the RCTs submitted for PMA approval, DES use was not associated with an increased rate of cardiac death and MI compared with controls, despite a numerical increased rate of late stent thrombosis; but it is possible that the number of patients studied was not large enough to permit the detection of a difference between treatment groups.

There is consensus that studies of larger numbers of patients followed over a longer period of time are needed. However, requiring much larger and longer trials to detect low-frequency events (such as stent thrombosis) before PMA submission can stifle the development and availability of improved devices for patients. Therefore, the FDA recommends that each sponsor design a large postapproval study that can be implemented quickly after DES approval.

The objectives of the postapproval study are to define the rate of stent thrombosis and the rate of cardiac death plus MI after DES implantation in patients treated in accordance with the intended use (on-label). The recommended primary endpoint of the postapproval study is the rate of stent thrombosis at 1 year. The sample size should be sufficiently large to confirm that the upper bound of the one-sided 95% confidence interval (CI) around the observed rate of stent thrombosis from 12 to 60 months after implantation is ≤1% for each yearly interval for patients treated in accordance with the labeled indication. To obtain an adequate sample size, subjects from the preapproval trials may be pooled with a cohort of patients in the postapproval study treated in accordance with the labeled indications for use. Follow-up should continue through 5 years after DES implantation to evaluate whether the DES thrombosis rate plateaus or continues to increase over time. This study-pooling approach provides increased precision around the observed event rate (ie, a narrower 95% CI) and offers confirmation that the DES meets the bar of a reasonable assurance of device safety.

A coprimary endpoint of the postapproval study should be an assessment of the rate of cardiac death and MI at 1 year after stent implantation in an on-label cohort of patients. This cohort can also be pooled with patients treated with the new DES in the preapproval pivotal study and compared with the control stent subjects in the pivotal trial.

In addition, postapproval studies play an instrumental role in assessing unanticipated adverse events and provide information on outcomes in real-world patient populations, including use outside the labeled indications. The rates of death, MI, stent thrombosis, need for repeat revascularization, and patterns of APT should be evaluated in these higher-risk patient and lesion subgroups.

CONCLUSION

DES represent an important advance in the treatment of coronary disease. High DES utilization rates based on a sustained reduction in arterial restenosis have been tempered somewhat by concerns over late thrombosis. The FDA and the clinical community have learned much about the risk-benefit of these devices since the first DES was approved, and insights gained have been incorporated into the draft DES guidance. Although the refinement of DES trial design and conduct may seem complex, the FDA's mission in the regulation of DES remains unchanged—to ensure the continued safety and effectiveness of medical products in the least burdensome manner for the benefit of patients in the US. To this end, the FDA encourages early and ongoing dialogue with stent manufacturers and clinician investigators during device development and trial design to ensure that new DES programs meet preclinical and clinical trial standards. ■

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