EuroIntervention

The FDA role in the development of percutaneous heart valve technology

Bram D. Zuckerman, MD; Wolf Sapirstein*, MD ChB.; Julie A. Swain, MD

U.S. Food and Drug Administration, Division of Cardiovascular Devices, Office of Device Evaluation, Center for Devices and Radiological Health, Rockville, MD, USA

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Introduction

During the past several decades changes to medical care have occurred at a geometrically increasing pace, nowhere more so than in the field of cardiovascular disease. This is readily apparent when looking at valvular heart disease. The earliest widely applied interventions were closed heart commissurotomy performed during the 1950's for relief of aortic, mitral, and pulmonic stenosis[1]. The introduction of extra-corporeal heart and lung bypass circulatory support in the late 1950's permitted these procedures to be performed under direct vision. There was however surprisingly little improvement in results until the successful introduction of a mechanical valve prosthesis in 1960 by the collaboration of Starr and Edwards and the use of allograft aortic replacements in 1962 by Barrat-Boyes[2,3]. This was also the period when Carpentier demonstrated that it was possible to repair a mitral valve and shortly thereafter in 1967 initiate the use of xenografts for biological tissue replacement of both the mitral and aortic valves[4,5]. This period of rapid change covered about two decades to be followed by thirty five years of improvement in devices but relative stagnation in surgical technique. With the new millennium came a sea change in the research directed at management of cardiac valve disease. Starting with adaptation of minimally invasive methods of performing conventional open heart surgery the focus changed to a search for entirely catheter-based treatments that aimed at duplicating established and successful open surgical procedures with totally closed, percutaneous methods.

Cribier introduced in 1984 the earliest percutaneous treatment for valve disease, with balloon valvoplasty duplicating the angioplasty so successfully employed in the coronary vasculature[6]. Bonhoeffer's report of the trans-venous deployment of a prosthetic valve in a failed pulmonary conduit in 2000 and Cribier's transvascular implant of a stented biological valve prosthesis following balloon valvoplasty of calcific aortic stenosis in 2002 set the stage for what has become an explosion in research and development of devices directed at this type of valve treatment. While none has been approved for marketing by the FDA as yet, some twenty different devices have been reported as under investigation at recent professional meetings[7,8].

FDA regulation of cardiovascular devices

The regulation of medical devices was introduced in the US with the 1976 Device Amendments to the Food, Drug, and Cosmetic Act of 1938[9] and in the European Union (EU), of similar population size and medical sophistication, with the Medical Devices Directives (MDD) issued by the European Commission in 1991[10]. While these two bodies approach device regulation somewhat differently, they have the similar objectives of ensuring that medical devices are

* *Corresponding author: Division of Cardiovascular Devices, Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration. 9200 Corporate Blvd., HFZ-450, Rockville, MD 20850, USA*
E-mail: Wolf.Sapirstein@FDA.HHS.gov

safe and effective for marketing and that they are made available to the health care environment expeditiously. So while this article primarily describes the FDA regulatory process, a limited comparison to that of the European community will permit the reader to make a judgment of the value cost for each. It should however be noted that the FDA, which is responsible for evaluating about 25 % of the gross national product of the USA, is considered by various commentators to be the most effective example of a consumer protective organization.

The FDA regulatory process

Pre-market regulation

The US employs a risk-based paradigm for classification of devices. Percutaneous Heart Valve (PHV) prostheses are placed in Class 3, the highest risk class for devices exhibiting the most serious consequences to patients in the event of device failure. An extremely rigorous evaluation is demanded by the FDA to assure that devices in this class perform with reasonable assurance of safety and effectiveness. Safety is pre-eminent in this examination and is clearly defined in relation to the intended function and indication for use. Effectiveness is not specifically defined but left in large measure for the Agency to determine on a device-by-device basis. Granting of Pre-Market Approval (PMA), necessary for commercial distribution of most cardiac prostheses, requires that valid scientific evidence support this determination of safety and effectiveness and that in a final analysis of this evidence, a risk-benefit evaluation indicates a clinical utility that can be labeled for the device. Such evidence is obtained from a U.S. clinical study for unapproved devices with an Investigational Device Exemption (IDE) granted by the Agency only after reasonable assurance of feasibility for the device performance and preliminary safety has been demonstrated with pre-clinical engineering test data and animal test data. The three faceted approach of preclinical bench testing, preclinical animal data and clinical testing provides the most complete information using the least time and resources. A hierarchical listing of trial design places a randomized control trial as providing the most robust information and one that the FDA believes is necessary for most new technology for treatment of cardiovascular conditions with permanent implants. This is therefore considered necessary for the evaluation of devices developed for the percutaneous treatment of valve disease as represented by Percutaneous Heart Valves (PCVs). A limited observational pilot or feasibility study may be permitted prior to the pivotal study. These stages in the approval process for valve prostheses are strictly monitored by the Agency. Final approval for marketing generally requires additional review by, and recommendations from, an advisory panel of outside experts discussed in an open public forum.

The FDA regulations are relaxed for unusual situations. A Humanitarian Device Exemption (HDE) permits the use of a device which has been designated by FDA as a Humanitarian Use Device (HUD). A HUD is defined as those indicated for no more than 4000 patients annually who are in a medically plausible subset and are without effective alternative device therapy. Reasonable evidence of safety and only probability of benefit are required for this exemption. Emergency Use is permitted for devices where urgency precludes FDA's prospective evaluation for appropriate entrance criteria. Emergency use is allowed even when a device is neither approved nor under study if there is proper clinical documentation of need. Compassionate Use is granted by FDA with clinical justification for patients not meeting entrance criteria for participation in an ongoing IDE trial or when no IDE trial exists.

Post-marketing regulation

Pre-market assessment occurs within the restricted parameters of a carefully controlled study. This is recognized as not necessarily reflecting performance in the real world of public health care. To this end the FDA has several tools for monitoring the marketing phase within the total life cycle of devices. The Agency can require that a Post-Approval Study be continued on the IDE cohort as a condition of marketing approval. This is generally required to answer questions related to issues not fully addressed in the IDE study, such as longer-term results and the occurrence of infrequently occurring events. Longer-term results can be obtained by further follow-up of the initial IDE cohort, or by enrollment of a new Post-Approval cohort. Infrequently occurring events usually require a larger Post-Approval cohort to be enrolled. The Agency can also require further information on the marketed use of the device in a new Post-Market Surveillance study. Such studies, conducted under an FDA approved protocol, will generally address questions such as "generalizability" of results, not available from the pre-market assessment. In addition sponsors are required to submit Annual Reports to the FDA detailing marketing experience with the device.

After marketing approval of a device, manufacturers must notify the FDA through Mandatory Device Reporting within 30 days of their becoming aware of device failures and device related deaths. MedWatch is a program for reporting of device failures and adverse events by end –users, distributors, and manufacturers.

The FDA has several options for responding to post market device reports of unacceptable performance. FDA can require that a manufacturer issue a "Dear Doctor" letter to advise users of modifications necessary for patient management, publicize information on an Internet web site and in professional Journals, and in extreme cases can require that a manufacturer issue a device recall. Rescinding a marketing approval is a rare action, instead voluntary withdrawal of sale by the manufacturer, for example as occurred with the Silzone treated mechanical valve prosthesis, is a more frequent response to any FDA finding of significant adverse device performance.

The European Union device regulation

The EU requires that member countries appoint a Competent Authority (CA) to implement the MDD's which are legislatively incorporated into the respective country's legal system. Such enactment can enlarge the conditions specified in the MDD but can not attenuate them. Devices are categorized according to risk, similar to the US, with cardiac devices placed in Class 3. Sponsors self-certify with a Technical File that they adhere to requirements set by a Standards Body established by each CA. This File is submitted to an independent party, the Notified Body (NB), designated by the CA

to approve the manufacturer's self-affixed CE label for marketing in all but Class 3 devices. In the case of Class 3 devices this Technical File is termed a Design Dossier and must be approved by the NB before the manufacturer can affix a CE mark for marketing. While not required by the MDD, a CA can require clinical studies, approved by member country's national and local ethical boards before accepting a CE certification by a NB of any country. A CE must be recognized by all countries unless additional study is required by a country or it is restricted for cause.

The EU has no formal system for post-market device monitoring but instead relies on clinical experience to define the specific role for a CE marked device. Guidelines have been developed in Europe, called the Medical Devices Vigilance System which provides information for reporting incidents. Clinical experience is sometimes obtained from registry data collected under the auspices of professional societies. Member countries however have the authority to undertake appropriate independent action to address problems. Such action can range from public health notifications to withdrawal from national marketing as occurred with the Silzone coated valve prosthesis by the British Department of Health.

Regulatory strategy for clinical trial design for percutaneous heart valves

The clinical trial required for a PHV IDE poses multiple complex challenges for the sponsor, FDA, and investigators. FDA recommends that sponsors initiate early interaction with the agency so that the difficult and controversial issues can be discussed prior to submission of an IDE. The next section will summarize key points to consider in preparing a clinical trial development plan for discussion.

Feasibility trial design

There are several purposes of the feasibility trial ; to establish preliminary safety and efficacy, to provide information for sample size estimations for the pivotal study, and to refine entrance criteria, to assess the operator learning curve, to refine the configuration of the device, and to test the adequacy of the Case Report Forms. The feasibly trial often is single-armed with less than 100 patients. The feasibly trial is occasionally preceded by a small trial to fine-tune device designs and patient inclusion criteria. It is important to collect data from the treating physician in the feasibly trial regarding what treatment would have been recommended to the patient if the experimental device was not used. This information will help determine the appropriate designation of the control group for the pivotal trial.

Pivotal trial design

It is expected that the pivotal trial for PHV's will be a randomized, controlled trial. Single-arm pivotal trials using historical data are generally not acceptable. The hypotheses for safety and efficacy must be clinically relevant and sample size calculations must be supported by data and literature references. When considering the design of PHV trials, collaboration between interventional cardiologists and cardiac surgeons is recommended. It is important when comparing percutaneous technology with an open surgical procedure to assure equivalent expertise of the practitioners. If there are study centres outside the US, the same protocol should be used as in the US.

Control group

The most difficult decision to make regarding the pivotal trial is the choice of control group. The choice of control group will determine the hypotheses to be tested (e.g. superiority or non-inferiority), the labeling claims permitted, the trial size, and the characteristics of the trial patients. Data from the feasibly trial will help determine the appropriate control group. For example, for percutaneous aortic valve replacement for aortic stenosis, possible control groups might be open surgery, balloon valvuloplasty, or medical treatment for patients who are not operative candidates or who are at an extremely high risk for open operation. It is important to remember that the control group to which patients are randomized must be a treatment for which there is clinical equipoise.

Inclusion/exclusion

Patient enrollment in the study must take into account the device design and method of deployment. For instance, the device must be compatible for deployment with the pathologic anatomy of patients recruited. These inclusion/exclusion criteria should also permit enrollment homogeneity of treatment and control arms. The particular characteristics of the device, such as anatomic requirements of the patient (e.g. annulus size, peripheral vessel characteristics, etc.), as well as the choice of control group, dictate many of the inclusion/exclusion criteria. For example, if the control group is open surgery, then the inclusion criteria should describe a patient population who would normally be referred for surgery.

Endpoint

Clinical trial design and endpoint selection depends on the type of device, the control population, and the intended use of the device. For mitral repair devices, repair to mild or better mitral insufficiency is an appropriate clinical surrogate endpoint. For valve replacement, the amount of stenosis and insufficiency is appropriate. Data on mid-term results to assess stability of the procedure is needed since for PHV's the durability in humans, the effect on heart failure progression, the effect of remaining mitral or aortic regurgitation on ventricular reverse remodeling, and the effect on the ability to do subsequent valve repair in mitral patients and replacement in aortic patients are unknown. Normally a 1-2 year endpoint with a 5-10 year follow-up will be required, depending on the intended function of the device and the indications for use.

Trial bias considerations

Since trials for PHV devices generally cannot be blinded, trial design should account, as much as possible, for recognized causes of trial bias such as positive and negative placebo effects, as well as selection, assessment and treatment bias.

Data analysis

Special data analysis and hypothesis considerations are encountered when designing trials comparing less invasive (but possibly safer) procedures with more effective invasive procedures. Close collaboration between the FDA and the sponsor is needed to jointly develop innovative trial designs.

Trial monitoring

Because of the novelty of PHV devices and the lack of long-term experience with these devices, close ("on-line") trial monitoring by an independent Data Monitoring Committee and a Clinical Events Committee is recommended.

FDA decision

The FDA is required to evaluate the risk versus the benefit of new devices when making decisions on approvability. Hopefully, a well-designed and well-carried out trial will be submitted to the Agency for consideration. However, simply meeting the prospective end-points in a trial does not assure approvability for the device if there are confounding aspects to the data.

Conclusions

Improving the process of device approval is an important goal for the FDA. There are several ways to ensure the smoothest regulatory process. First and foremost is early collaboration with FDA to address and resolve issues regarding important aspects of the approval process. The process by which the FDA works with industry early in device development is the pre-IDE process. In order to expeditiously gain approval to proceed to clinical testing of a new device, it is important for the sponsor to carefully consider and address the FDA concerns that are raised in pre-IDE discussions.

Sufficient safety evidence is needed to begin clinical studies in the US and most disapprovals are based on inadequate bench and/or animal testing. Finally, the science of clinical trial design requires innovative approaches for these innovative devices; working collaboratively with the Agency will speed the entire process.

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