The Role of Clinical Trials in the Food and Drug Administration Approval Process for Cardiovascular Devices

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The Food, Drug and Cosmetic Act of 1938 (the Act) required manufacturers to provide evidence of safety to the Food and Drug Administration (FDA) before drugs could be marketed. Amendments to the Act in 1962 added the requirement of demonstration of effectiveness to the condition for approval (21 CFR 314).1 The Medical Device Amendments of 1976 extended these controls to devices, establishing a tiered system of classification based on the level of controls required to ensure safety and effectiveness before marketing a device (43 FR 32988).2 Devices with performance characteristics that are life sustaining, the failure of which presents unreasonable risk of injury or illness, are required to undergo premarket approval, with sponsors providing valid scientific evidence to support claims for safety, effectiveness, and utility. The most recent amendments to the Act were introduced with the Safe Medical Devices Act (SMDA) of 1990 and Medical Device Amendments of 1992.

Among other issues, the SMDA addresses the need to monitor “chronic” function and safety through discretionary or required postmarket surveillance of devices using scientifically designed studies (21 CFR 821). The SMDA thus recognizes that the premarketing approval process may need to be supplemented by assessment of long-term performance of devices. The need for such programs was underscored by the late failure of prosthetic heart valves.3

The FDA’s role, thus, is to ensure that marketed devices are safe and effective and have demonstrable clinical utility. The approval process for “significant risk” devices may take one of two routes. A premarket notification [510(k)] requests marketing clearance for devices demonstrated to be substantially equivalent in technology and function to a device marketed before the 1976 amendments. A premarket approval application (PMA) is required for Class III (significant risk) devices or devices marketed subsequent to this amendment. Although device approval under 510(k) procedures may not require clinical trials, devices requiring a PMA must undergo more stringent documentation of safety and efficacy with data that are scientifically derived, using acceptable laboratory (in vitro and in vivo) and clinical studies. The regulations (21 CFR 860.7) spell out in hierarchical fashion what constitutes “valid scientific clinical evidence.” The controlled clinical trial, academically acknowledged as the experimental gold standard for clinical studies, is afforded preeminence.4,5

Controversial Issues

There is little dispute within the clinical community regarding the nonclinical requirements for PMA approval. Debate centers on the stringency of the clinical evidence demanded and concerns that this may unreasonably constrain clinical judgment and physician choice during the trials and unnecessarily delay the introduction of therapeutic advances beneficial to health care. These arguments primarily target requirements for randomized controlled clinical trials. (The differing views regarding the precise role for these trials are discussed in companion editorials.)

The FDA’s Position

It must be clearly stated that although requiring the regulatory agency to adjudicate on the clinical safety and efficacy of medical devices before allowing commercial marketing, the Act prohibits interfering in patient care and clinical judgments associated with medical practice, the domain of the peer review and staff accreditation process.6

The FDA requires that clinical data submitted in support of a PMA application meet a standard of scientific evidence acceptable for peer review. A panel of clinical experts in the field of the device’s application will examine the scientific submission in support of the PMA application and, on the basis of that evidence, make its recommendation to the FDA regarding marketing approval. The Advisory Panel has usually requested a clinical trial, randomized for control of bias, to generate this evidence.

PMA Protocols

Performance of the clinical study requires application to the FDA for an investigational device exemption (IDE) to permit clinical use of an unapproved device. The proposed study must also be approved by the local institutional review board.

The agency provides information in draft guidance documents outlining the type of information generally required to demonstrate device safety and efficacy and the acceptable study designs to generate this data for PMA applications. These documents are supplemented

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with iterative consultations with sponsors and investigators. However, it is the responsibility of the sponsor to develop and submit an appropriate study protocol. It should be emphasized that the investigators, with their clinical and scientific background, must assume intellectual responsibility for participating in and advising the sponsors on the design of any protocol in which they will be involved in executing.

An initial pilot (feasibility) study may be recommended or required to define the end points and refine methodology for the definitive clinical study.

The regulations for premarket clinical device testing were adapted from those for the drug model. However, provision is made for peculiarities associated with device testing. Examples of these are the difficulties in implementing blinded studies, the ethical constraints on “sham” procedures to provide placebo controls, and the difficulties inherent in using approved devices as active controls. Recognizing these differences, the agency has therefore readily considered alternatives to a randomized active concurrent control for study design when provided with clinical and statistical justification. This flexibility was evident at recent workshops sponsored by the Center for Devices and Radiological Health to discuss the role and improve the general quality of clinical trials in device evaluation. Comments from a broad spectrum of interested parties involved in the medical device field were incorporated in draft guidance documents for cardiac prosthetic valves and interventional cardiology devices presented by the Division for Cardiovascular, Respiratory and Neurological Devices. These two device categories illustrate the unique problems encountered in designing trials for devices that while adequately controlling for bias do not unrealistically encumber the protocol.

The stringency of requirements for implanted devices as contrasted to those for interventional therapy is exemplified in the above guidance documents. A further difference is encountered in the requirements for life-sustaining devices for end-stage disease, where no alternative therapy is available. In illustration of the latter, data on safety and efficacy for cardiac-assist devices to wean patients from cardiopulmonary bypass have been accepted based on a reasonable probability of success.

**Prosthetic Cardiac Valves and Interventional Cardiology Devices**

The progress achieved over the past 30 years in the development and design of prosthetic cardiac valves has resulted in an extremely low complication rate over the short term. As a consequence, the magnitude of a randomized controlled clinical trial to evaluate any new prosthetic heart valve and provide statistically meaningful data acquires proportions beyond what can be reasonably achieved with the relatively low incidence of prosthetic valve replacement. Thus, the guidance document for valve prostheses has accepted the concept of an observational study protocol design with data analysis based on patient risk–related objective performance criteria developed from historical data. Preliminary in vitro and in vivo studies become even more important with this study design, and an initial clinical pilot study may be required. The SMDA of 1990, in providing for required and discretionary postmarketing surveillance studies with device-tracking requirements, enables the monitoring of and prompt response to chronic device performance.

The draft guidance document relating to interventional cardiology devices illustrates situations where randomized controlled clinical trials are essential to establish safety and efficacy. Because treatment benefit for many of these devices is dependent on subjective assessments, concurrent randomization of the controls is essential. The potential for selection and assessment bias is also considerable, and increasing importance is therefore being placed on blinded core laboratory analysis of assessment data, such as angiograms. In the case of devices that are insignificant configuration modifications to approved devices, such as angioplasty catheters with minor changes in balloon length, these requirements could reasonably be relaxed. Once a PMA is approved, new indications for a device may become apparent when use is generalized to the target population. Appropriate labeling changes to accommodate these indications can then be sought with a PMA amendment based on valid scientific evidence.

**The Randomized Controlled Clinical Trial: The FDA’s Perspective**

The above examples demonstrate that the agency, while accepting the randomized controlled trial as the study of choice for evaluating a device, recognizes situations where other valid models of trial design may be more appropriate. When alternative therapy is not available, ethical considerations may preclude a randomized trial of a device for treatment of life-threatening conditions. However, because all interventions involve some risk, the benefit of close attention and monitoring that patients receive in a clinical trial may be the best justification for a randomized clinical trial. The agency will work with sponsors and the clinical community to develop the most scientifically appropriate alternative to a randomized controlled trial when evidence of this need is convincingly demonstrated. Thus, nonrandomized concurrent controlled trials, or even observational studies based on sound historical data with acceptable confidence intervals for results, may be considered valid trials. Circumstances may necessitate studies in the form of observational trials based on historically derived objective performance criteria, with statistical testing of confidence intervals and “proving the null hypothesis.”

The FDA's review of PMA applications has been criticized as cause of inordinate delays in the general availability of medical devices. The agency has implemented several measures to streamline the process and accelerate new device approval. These include the triage of applications to a three-tiered level of review intensity, depending on device risk, and an expedited review for devices for which there is an urgent clinical need. Of possible equal importance in reducing review time is the introduction of a “refuse to accept” policy for submissions that are patently deficient. This provides sponsors with a prompt response and initiates interaction between sponsor and regulatory scientists.

**Summary**

An innovative medical device industry has been pivotal in the phenomenal impact of technology on health...
care, and its vitality is critical to continued progress in this field. The Office of Device Evaluation is aware of the deleterious impact that delays in approval can have on both industry and health care.

"Off-shore" device production and clinical studies are subject to the same FDA regulatory scrutiny for marketing approval in the United States. Indeed, many overseas jurisdictions have adopted FDA regulations separately or as part of the International Standards Organization recommendations. Although clinical studies performed outside the United States may be acceptable, the agency requires the study cohort for a device trial to demographically approximate the targeted US population.

The agency solicits input from all interested parties in developing guidance for the review process. Guidance is generated in consultative interaction among device sponsor, clinical investigators, the regulatory agency, and other interested parties. This cooperation ensures a dynamic review process capable of keeping pace with changes in the field.

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Circulation. 1994;89:1900-1902
doi: 10.1161/01.CIR.89.4.1900

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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