

# Premarket Clinical Evaluation of Novel Cardiovascular Devices: Quality Analysis of Premarket Clinical Studies Submitted to the Food and Drug Administration 2000–2007

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The quality of clinical data submitted by manufacturers to support Food and Drug Administration cardiovascular device premarket approval (PMA) applications varies widely and formal quality assessment has not been previously performed. This study evaluated all original cardiovascular device PMAs with Food and Drug Administration decisions between January 1, 2000, and December 31, 2007, to assess the quality of clinical investigations submitted by manufacturers. Effectiveness and safety end points were judged high quality if they were clearly defined and associated with a specific time point for analysis. Subject accounting was high quality if 90% or greater of the original cohort was accounted for at study conclusion. In total, 88 cardiovascular device PMAs (77.3% permanent implants), 132 clinical studies, 37,328 study subjects (age  $61.0 \pm 14.5$  years, 33.9% women, 86.3% white), and 29,408 device recipients were analyzed. All PMAs contained clinical data. Primary effectiveness end points, primary safety end points, and subject accounting were deemed high quality in 81.8%, 60.2%, and 77.3% of pivotal studies, respectively. Key cardiovascular comorbidities (coronary artery disease 51.1%, diabetes 36.6%, hypertension 35.2%, heart failure 37.5%, tobacco use 31.8%) and race (14.8%) were infrequently reported, and studies rarely included patients younger than 18 years of age (10.2% of studies). Poorly defined safety and effectiveness end points, poor patient accounting, and incomplete collection of important patient comorbidities make device safety and effectiveness assessments more challenging. Women, pediatric, and nonwhite populations are underrepresented in premarket cardiovascular clinical trials. Manufacturers, regulators, and the clinical community should collaborate to address these study shortcomings to ensure that patients are treated with reliable, safe, and clinically useful medical devices.

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The opinions expressed in this article are those of the authors and do not necessarily represent the practices, policies, positions, or opinions of the FDA.

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## INTRODUCTION

The Food and Drug Administration (FDA) is responsible for evaluating the safety and effectiveness of medical devices marketed in the United States. The premarket evaluation process, which is based on the FDA's regulations, varies according to the complexity of the device and the degree of risks to the intended patient population. Devices are categorized into three regulatory classes (I, II, and III).<sup>1–3</sup> All devices are subject to "general controls," including proper labeling and adherence to predefined Good Manufacturing Practices such as a demonstration of adequate packaging and

storage.<sup>4,5</sup> Class I devices are low-risk devices whose regulation is generally based on general controls alone. Class II devices are moderate-risk devices; in addition to general controls, they must meet or exceed certain predefined product performance standards. Most Class II devices are subject to premarket notification [510(k)] in which equivalence in terms of safety and effectiveness to similar devices is demonstrated. Products categorized as Class III are devices that present the highest level of risk such as pacemakers and coronary stents. The reasonable assurance of their safety and effectiveness is demonstrated by a thorough premarket evaluation and approval process.<sup>5</sup>

Most Class III devices enter the market through the Premarket Approval (PMA) Application process. This process involves FDA's analysis of information about device safety and effectiveness; the specific data required depend on the device. PMA applications include information on design, engineering, manufacturing, biocompatibility, other nonclinical laboratory testing, and animal studies in addition to human clinical investigations, which may range from observational studies to prospective, randomized clinical trials.<sup>1</sup> The clinical study design and data necessary to support the specific Class III device depend on the scientific questions that need to be addressed with the new device.

In an effort to expedite the device review process and bring new, important technologies to patients as soon as possible, Congress mandates that the FDA use a "least burdensome" approach to device evaluation.<sup>6,7</sup> The FDA may require submission of only that data it deems necessary to demonstrate a reasonable assurance of safety and effectiveness. This has important implications for clinical trial design, including size, duration, safety and effectiveness end points, the selected control populations, and the prespecified statistical plan.

By law, the FDA must render a decision on a PMA application within 180 days.<sup>7</sup> Applications that are incomplete or that contain data from poorly conducted clinical studies may result in deficiency letters that can delay the Agency's ability to fully evaluate the device application and can delay or prevent its ultimate approval.

This quality assessment study was designed to provide a quantitative description of preapproval study subjects and clinical trials. The goals were to: 1) quantify the size and duration of clinical studies presented in PMAs; 2) describe study subject demographics and identify underrepresented populations; 3) define and quantify fundamental study quality measures; and 4) guide data-driven refinement of both the structure and content of pre- and post-approval clinical investigations.

## METHODS

### Study selection and data extraction

All original cardiovascular device PMAs with decisions between January 1, 2000, and December 31, 2007, were included in the study (N = 88). PMA supplements and products submitted through the 510(k) notification process were not included. Applications were identified through the FDA database.<sup>8</sup> Relevant data were extracted from the individual PMAs to obtain details regarding the data fields of interest for the study.

Each PMA application was reviewed to assess the following: 1) device characteristics (intended use, intended patient population, permanence, manufacturer); 2) subject characteristics (demographics, comorbidities); 3) clinical study features (design, size, duration, safety and effectiveness end points, control populations, statistical plan); and 4) clinical study quality. Devices were grouped into three categories: interventional cardiology (eg, coronary and peripheral stents, vascular access closure devices), electrophysiology (eg, ablation catheters, pacemakers), and cardiac surgery (eg, heart valves, surgical adhesives).

### Assessment of study quality

Clinical studies were assessed for the following quality measures: quality of effectiveness end point, quality of safety end point, and quality of subject accounting. Effectiveness and safety end points were considered to be of high quality if the manufacturer identified and defined the end point and it was associated with a specific time point for analysis. An example of a high-quality end point would be "Major Adverse Cardiac Events at 6 months" with Major Adverse Cardiac Events defined as death, myocardial infarction, or urgent revascularization. Subject accounting was considered to be of high quality if the manufacturer provided a thorough description of patient enrollment and follow up. Specifically, 90% or greater of the original cohort had to be accounted for at the conclusion of the study (ie, less than 10% loss to follow up). Blinding and randomization were not included in the study quality assessment because in many cases, it is not possible and/or ethical to implement these study design characteristics in medical device trials.

### Statistical analysis

Statistical analysis was performed using SAS (Version 9.1; SAS Institute, Cary, NC). Discrete and continuous variables were analyzed by chi square and Student *t* test, respectively. *P* values of < 0.05 were considered to be statistically significant.

## RESULTS

During the study period, 88 original PMAs assessing 88 devices from 42 different manufacturers were analyzed (Table 1). These applications included 132 clinical studies involving 37,328 study subjects and 29,408 device recipients. Clinical data were submitted in support of every PMA application. Pivotal clinical studies ranged in size from 16 to 1492 device recipients and in median duration from 1 to 62 months (Table 2). Subject characteristics as reported in the *largest* clinical study in each PMA are described in Table 3. The average age of study subjects was 61.0 ± 14.5 years, with 33.9% women represented. Subject race was reported in 14.8% of studies. When race was reported, subjects were 86.3% white.

Key cardiovascular comorbidities in the largest study contributing to each PMA were frequently not reported (Table 3). For example, the presence of coronary artery disease was reported in only 51.1% of PMAs, diabetes in 36.6%, hypertension in 35.2%, congestive heart failure in 37.5%, and smoking in 31.8%.

### Quality assessment

The primary effectiveness end point was assessed as high quality in 81.8% of studies, and the primary safety end point was high quality in 60.2% (Table 4). Both were of high quality in 56.8% of studies. Examples of poor quality end points are given in Table 5. Subject accounting was high quality in 77.3% of studies (Table 4).

## DISCUSSION

Premarket device evaluation is critical for ensuring that only safe and effective medical devices are marketed. The FDA uses the PMA process to evaluate high-risk medical devices to determine their safety and effectiveness before permitting them to be marketed in the United States. This process includes a thorough evaluation of device design, manufacturing,

biocompatibility, and preclinical and clinical testing. This study quantitatively describes the characteristics and quality of the premarket clinical studies submitted to the FDA for consideration during the cardiovascular device approval process. The study findings demonstrate that submitted studies frequently lack important details, including information about study subjects and study end point definitions.

To safely and effectively apply a device therapy to a patient, it is critical to understand the types of patients in whom the device has been studied. From 2000 to 2007, detailed subject characteristics were often incompletely reported in premarket clinical studies submitted to support cardiovascular device PMA applications. For example, history of coronary artery disease, diabetes, hypertension, heart failure, and smoking were reported less than half the time. Only one in seven studies reported subject race. For studies that did report demographic information, women, pediatric populations, and nonwhite participants were underrepresented. These limitations challenge the creation of broadly applicable labeling and instructions for use and can make it difficult to predict “real-world” device performance when a product is applied to a more diverse patient population. Efforts to more completely report patient demographics and comorbidities and to enroll more representative patient populations could overcome these shortcomings. In some instances, the Agency is able to determine that the device warrants approval but that these additional questions may be further investigated postapproval in the form of registries or postmarket clinical studies.

Not unexpectedly, clinical studies submitted to support cardiovascular device premarket approval applications varied widely in size, duration, and study design. This reflects the broad range of devices submitted for marketing approval from one-time use objects like cardiac arrhythmia ablation catheters to permanent implants such as coronary stents. There is no specific study size, study duration, or study design that applies to all premarket device evaluations.

**Table 1.** Device and application characteristics.

|   | Interventional | EP         | Surgery    | Total      | P Value |
|---|----------------|------------|------------|------------|---------|
| Total number of PMAs, N                 | 42             | 29         | 17         | 88         | —       |
| Permanent implants, N (%)               | 37 (88.1)      | 14 (48.3)  | 17 (100)   | 68 (77.3)  | a, b    |
| PMAs with clinical data, N (%)          | 42 (100)       | 29 (100)   | 17 (100)   | 88 (100)   | —       |
| PMAs using randomization, N (%)         | 20 (47.6)      | 11 (37.9)  | 4 (23.5)   | 35 (39.8)  | —       |
| Clinical studies per application (mean) | 1.69 ± 1.1     | 1.21 ± 0.5 | 1.53 ± 0.5 | 1.50 ± 0.8 | a, b    |

PMA, premarket approval application; a,  $P < 0.05$  for comparison of interventional versus electrophysiology (EP) groups; b,  $P < 0.05$  for comparison of EP versus surgery groups; c,  $P < 0.05$  for comparison of interventional versus surgery groups.

**Table 2.** Study characteristics.

|  | Interventional | EP            | Surgery       | Total         | P Value* |
|--|----------------|---------------|---------------|---------------|----------|
| Number of PMAs   | 42             | 29            | 17            | 88            | —        |
| Number of study subjects (mean ± SD)                     | 485.6 ± 498.6  | 283.2 ± 152.4 | 512.8 ± 521.5 | 424.2 ± 429.7 | a        |
| Number of device recipients (mean ± SD)                  | 352.8 ± 363.4  | 228.5 ± 118.4 | 468.5 ± 543.6 | 334.2 ± 358.4 | a        |
| Number of subjects in largest study (mean ± SD)          | 356.9 ± 282.0  | 275.9 ± 156.6 | 418.9 ± 422.2 | 342.2 ± 284.4 | —        |
| Number of device recipients in largest study (mean ± SD) | 246.9 ± 149.8  | 221.1 ± 122.1 | 374.5 ± 445.1 | 263.1 ± 234.4 | —        |

PMA, premarket approval application; SD, standard deviation; a,  $P < 0.05$  for comparison of interventional versus electrophysiology (EP) groups; b,  $P < 0.05$  for comparison of EP versus surgery groups; c,  $P < 0.05$  for comparison of interventional versus surgery groups.

Premarket clinical study design must be tailored to the specific device, its intended use, and the intended patient population.<sup>9</sup> In some cases, when well-accepted surrogate clinical end points such as Major Adverse Cardiac Events exist, shorter studies may be appropriate. In other cases, longer or larger studies may be required.

Unlike drug studies, in which placebo-controlled, double-blind methodology may be routinely implemented, clinical evaluation of devices is more challenging. It is sometimes not possible to blind the

investigators or patients (for example, for a study evaluating a left ventricular assist device). Similarly, randomization is not always possible or may not be warranted. Among the PMAs studied, 40% included randomized trials. Importantly, Congress mandates a least burdensome approach, and in some cases, alternative trial designs may be sufficient to provide evidence of reasonable assurance of safety and effectiveness. This may be true when well-established performance expectations exist, when satisfactory comparison groups are lacking, or under other circumstances.

**Table 3.** Subject characteristics.

|  | Interventional | EP          | Surgery     | Total       | P Value |
|--|----------------|-------------|-------------|-------------|---------|
| Number of PMAs   | 42             | 29          | 17          | 88          | —       |
| Age (mean ± SD)  | 57.5 ± 19.4    | 62.4 ± 7.3  | 67.3 ± 6.4  | 61.0 ± 14.5 | b,c     |
| Studies with some subjects aged younger than 18 years, N (%) | 4 (9.5)        | 2 (6.9)     | 3 (17.7)    | 9 (10.2)    | —       |
| Women, %†  | 37.4 ± 13.0    | 29.2 ± 16.3 | 33.3 ± 13.0 | 33.9 ± 14.8 | a       |
| PMAs reporting race, N (%)                                   | 9 (21.4)       | 1 (3.5)     | 3 (17.7)    | 13 (14.8)   | a       |
| White subjects, % ± SD‡                                      | 84.6 ± 8.5     | 96.9 ± 0    | 88.5 ± 2.1  | 86.3 ± 8.2  | —       |
| Studies reporting clinical characteristics*                  |                |             |             |             |         |
| CAD, N (%)   | 26 (61.9)      | 10 (34.5)   | 9 (52.9)    | 45 (51.1)   | a       |
| Diabetes mellitus, N (%)                                     | 25 (59.5)      | 1 (3.5)     | 6 (35.3)    | 32 (36.6)   | a,b     |
| Hypertension, N (%)  | 21 (50.0)      | 3 (10.3)    | 7 (41.2)    | 31 (35.2)   | a,b     |
| CHF, N (%)   | 9 (21.4)       | 12 (41.4)   | 12 (70.6)   | 33 (37.5)   | c       |
| Smoking, N (%)   | 21 (50.0)      | 1 (3.5)     | 6 (35.3)    | 28 (31.8)   | a,c     |
| Patient comorbidities*                                       |                |             |             |             |         |
| CAD (%), mean ± SD   | 76.5 ± 33.2    | 64.3 ± 21.6 | 43.2 ± 13.2 | 67.1 ± 30.4 | b,c     |
| Diabetes mellitus (%), mean ± SD                             | 29.3 ± 8.8     | 36.4 ± 0    | 24.9 ± 13.4 | 28.7 ± 9.7  | —       |
| Hypertension, mean ± SD                                      | 72.1 ± 18.5    | 55.1 ± 8.6  | 50.0 ± 22.5 | 65.4 ± 20.8 | c       |
| CHF, mean ± SD   | 12.0 ± 9.5     | 80.8 ± 34.8 | 55.0 ± 47.5 | 52.6 ± 44.5 | a,c     |
| Smoking, mean ± SD   | 45.4 ± 31.4    | 66.0 ± 0    | 74.3 ± 18.9 | 52.3 ± 30.8 | c       |

\*Data reported for the largest study included in each PMA.

†Mean percentage of women among pivotal studies reporting sex.

‡Mean percentage of white subjects among pivotal studies reporting race.

PMA, premarket approval application; SD, standard deviation; CAD, coronary artery disease; CHF, congestive heart failure; a,  $P < 0.05$  for comparison of interventional versus electrophysiology (EP) groups; b,  $P < 0.05$  for comparison of EP versus surgery groups; c,  $P < 0.05$  for comparison of interventional versus surgery groups.

**Table 4.** Quantitative study quality.

|  | Interventional | EP        | Surgery   | Total     | P Value |
|--|----------------|-----------|-----------|-----------|---------|
| Number of PMAs                                       | 42             | 29        | 17        | 88        | —       |
| High-quality primary effectiveness end point,* N (%) | 37 (88.1)      | 27 (93.1) | 8 (47.1)  | 72 (81.8) | b,c     |
| High-quality primary safety end point,* N (%)        | 24 (57.1)      | 23 (79.3) | 6 (35.3)  | 53 (60.2) | b       |
| High quality both end points, N (%)                  | 21 (50.0)      | 23 (79.3) | 6 (35.3)  | 50 (56.8) | a,b     |
| High-quality subject accounting,† N (%)              | 37 (88.1)      | 20 (69.0) | 11 (64.7) | 68 (77.3) | a,c     |

\*Effectiveness and safety end points were considered to be of high quality if the manufacturer identified and defined the end point and it was associated with a specific time point for analysis.

†Subject accounting was considered to be of high quality if the manufacturer provided a thorough description of patient enrollment and follow up. Specifically, 90% or greater of the original cohort had to be accounted for at the conclusion of the study (ie, less than 10% lost to follow up).

a,  $P < 0.05$  for comparison of interventional versus electrophysiology (EP) groups; b,  $P < 0.05$  for comparison of EP versus surgery groups; c,  $P < 0.05$  for comparison of interventional versus surgery groups.

Certain key, basic concepts, however, apply to the design and conduct of premarket clinical studies supporting PMA applications. Incorporating these features is both consistent with a least burdensome approach and can potentially avoid unnecessary delays in the premarket application process. Specifically, well-defined primary safety and effectiveness end points, including a specific statement regarding the time point at which they will be evaluated, should be provided. This study demonstrates that safety and effectiveness end points are often not defined with precision. The primary effectiveness end point was judged high quality in three fourths of studies, and the primary safety end point was high quality in just over half. In addition, study end points frequently lacked clear definitions, explicit time points, and clarity regarding the relative contribution of end point components. In addition, detailed patient accounting, which is critical to study interpretation, was deemed less than high quality according to our prespecified criteria in one fourth of cases. This can make statistical analysis of the

PMA data challenging and clinical application of the study results problematic.

This study has several limitations. Only original cardiovascular PMAs were evaluated during the study period. The applicability of these data to noncardiovascular PMAs and to devices submitted through PMA supplements is not known. Nevertheless, the principles outlined in this report should generally apply to all premarket clinical studies.

Specific to the cardiovascular program area, the Agency finds these results compelling and complementary to ongoing initiatives to better assess underrepresented patient populations of interest such as women<sup>10</sup> and children.<sup>11</sup> It is expected that this quality study will enhance the ongoing initiatives to increase the quality of clinical evidence to support new cardiovascular technologies. To be successful, these efforts need to be implemented in such a way that engages the clinical community and regulated industry in a transparent manner so that all constituents appreciate the benefit to patients and in the advancement of medical devices.

**Table 5.** Examples of study quality measures: end point definition.

|   | Criticism  | Proposed correction  |
|---|--|--|
| <b>Effectiveness end point</b>  |  |  |
| Device-related adverse events   | Specific identification of adverse events to be included in primary analysis not provided                  | Clearly identify and define specific adverse events that will be included in end point |
| Major Adverse Cardiac Events (MACE) at 30, 90, 270, and 360 days        | Specific time point for primary analysis not stated  | Clearly state specific time point for end point analysis                               |
| <b>Safety end point</b>   |  |  |
| Deaths, major in-hospital adverse events, device-related adverse events | Multiple end points of interest, no single component or combined events specified as the primary end point | Clearly state primary versus secondary end points                                      |
| Clinical data at 3 and 6 months   | Time point for primary analysis not stated   | Clearly state time point for end point analysis  |

Premarket clinical study design and conduct shortcomings may have a detrimental impact on the device approval process. Poorly defined safety and effectiveness end points, absent patient demographics and comorbidities, and poor patient accounting make study interpretation and assessment of safety and effectiveness more difficult. In contrast, well-conducted clinical trials lessen the burden on manufacturers, may accelerate the device approval process, and can benefit the public by bringing novel devices to market safely and more quickly. Manufacturers, regulators, and the clinical community must continue to collaborate to provide patients with reliable, safe, and clinically useful medical devices that meet appropriate benchmarks of clinical trial data quality.

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