Guidance to Sponsors on the Development of a Discretionary Postmarket Surveillance Study for Permanent Implantable Cardiac Pacemaker Electrodes (Leads)

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for Cardiac Pacemaker Leads
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INTRODUCTION

One of the provisions of the Safe Medical Devices Act of 1990 (SMDA) provided for discretionary postmarket surveillance (DPS) studies. The Food and Drug Administration (FDA) has decided to use this provision to require the submission of additional data about the safety and effectiveness of permanent implanted cardiac pacemaker electrodes (leads). At this time, the FDA has determined that the legal entity who has received clearance to market through submission of the premarket notification (510(k)) or premarket approval (PMA) application for a particular lead (hereinafter referred to as sponsor) will have primary responsibility for conducting postmarket surveillance of that lead. All others who are involved in the distribution of these devices will be responsible for ensuring that any data or information in their possession is made available to the sponsor of a DPS protocol. For example, a company may be required to provide the sponsor with information on the materials supplier or sales and distribution data so that the lead performance may be assessed by the sponsor through patient follow-up.

This document will provide guidance to sponsors on the design of a study protocol which will be submitted to the FDA for approval. Please note that data must continue to be collected and reported to maintain compliance with postapproval requirements (21CFR814) and Medical Device Reporting regulations (21CFR803).

FORMAT OF SUBMISSION

Each sponsor shall submit a study protocol which conforms to the following outline and addresses all issues in this guidance document.

Postmarket Surveillance Study Outline

Cover Letter to the FDA (identifying document as a DPS protocol)

I. Organizational and Administrative Information

A. Sponsor Information
   1. Sponsor's name and address
   2. Contact person's name, address, and telephone number

B. Table of Contents

C. Grouping and Exemption of Lead Models

D. Device-Specific Information
   For <u>each</u> lead model group:
   1. List of all lead model numbers included in the group with corresponding trade names
   2. Manufacturers' names and addresses, if different from sponsor
   3. Premarket notification or premarket approval numbers (original or supplement) under which devices were first marketed
   4. Document numbers for any other premarket approval application or premarket notification submission related to the devices

5. Dates that devices were in commercial distribution OR that devices were implanted in the United States
6. Numbers of leads distributed for each lead model in the group
7. Description of the devices

II. **Surveillance Protocol**

A. Study Objectives
B. Definitions of Terms
C. Study Design
   1. Description of Study
   2. Sample Size
   3. Data Collection Plan and Forms
   4. Follow-up Plan
   5. Data Quality Control
   6. Length of Study
   7. Data Analysis

D. Reporting Plan

III. **Principal Investigator**

A. Discussion of pertinent qualifications and experience
B. Curricula Vitae
C. Investigator Agreement
D. Disclosure of Financial Interests

IV. **Informed Consent and Institutional Review Board Considerations**

V. **Attachments**

A. Methodology for analyzing lead failures
B. Methodology for explanted lead analysis
C. Methodology for statistical analysis
D. List of leads for which exemptions have been granted or are pending
E. List of leads which you manufacture or market, but for which you do not have primary responsibility

SPECIFIC REQUIREMENTS

I. **Organizational and Administrative Information**

A. Sponsor Information:
This section should identify the legal entity (e.g., company) who is responsible for conducting the DPS study. The contact person may be an employee of the sponsor or may be a consultant or attorney hired by the sponsor.

B. Table of Contents:
The table of contents must identify the pages on which each section of the protocol may be found, in accordance with the format described above. Pages must be consecutively numbered from beginning to end, not by section.

C. Grouping and Exemption of Lead Models:
The FDA notes that there is considerable variation in the interpretation of the term "model" among sponsors. For the purposes of data collection and analysis, the FDA has determined that ***similar lead models should be combined, and be referred to as "groups."*** However, broad groupings, such as all leads with silicone insulation, would not be appropriate. In addition, if there have been significant design, manufacturing, or material changes, without a change in model designation, it may be necessary to study separate subsets of patients for the different variations of that model. The criteria which are used to establish lead model groups shall be used uniformly for both grouping and exemption requests. ***The FDA cautions sponsors that requests for exemptions cannot be granted for any individual lead model that can be grouped, unless the group as a whole would qualify for an exemption.***

1. Grouping:
The FDA recognizes that certain characteristics would not be expected to cause differences in device performance among similar leads. At this time, the FDA has determined that catheter length and connector type are such characteristics. Therefore, lead models of different lengths and connector types of the same basic lead shall be considered a "group." To avoid confusion, sponsors should use the term "lead model group" to describe one or more models of leads of the same materials, cross-sectional configuration, and electrode tip, with variation only in catheter length and connector type. The FDA will consider the effect of other variations in characteristics on the ability to group lead models on a case-by-case basis. Within a lead model group, the sponsor may determine which lead models will be included in the data collection and this information will be provided in the table requested under "Device Description."

2. Exemptions:
The FDA recognizes that, in order to obtain statistically valid results, data must be collected for a minimum number of leads for each lead model group. Commercial distribution status and the number of leads sold in the United States (during the entire marketing history) for each lead model group must provide the basis for any exemption request. ***At this time, the FDA will grant a request for exemption from the requirement to conduct a DPS study for a particular lead model group if all of the lead models in the lead model group are no longer sold as of August 1, 1993 and the total number of leads sold for that lead model group does not exceed 500.*** The request must be supported by written

documentation or certification that lead model group distribution did not exceed 500.

Requests for exemption of lead model groups that are no longer distributed with a total distribution greater than 500 must be supported by data that demonstrate that the availability and quality of retrospective data will not yield statistically valid information.

The FDA will not grant an exemption for any lead model group remaining in commercial distribution after August 1, 1993. If a previously discontinued lead model is again sold in the U.S. under the same model number, then that lead model will be subject to discretionary postmarket surveillance. A lead model introduced into commercial distribution under a new model number, whether or not a 510(k) is submitted, will be subject to required postmarket surveillance.

D. Device Description:
The information requested should be provided in tabular form (see attachment 1). The sponsor shall describe the pacemaker lead model group with sufficient detail to the person responsible for ensuring that the appropriate failure analyses are done and to the FDA to permit factors that correlate with device failure to be identified. Since the lead insulation has been implicated in past device complications and failures, the sponsor shall provide all available information about the insulation including lead design, manufacturing process, materials and biocompatibility, lead supplier, and basis for batch differentiation. The sponsor shall also maintain copies of promotional literature, labeling, physician's manuals, and training materials. While it is not necessary to submit these materials at this time, the FDA may request this information to aid in the evaluation of lead performance. Any confidential information should be labeled as such. The sponsor shall include the following:

Designation of lead model group, identifying the lead models within the group

Type of lead (eg., atrial or ventricular, bipolar or unipolar)

Electrode fixation method and description (eg., screw-in), including diagram

Lead insulation material(s), general and specific (inner and outer for bipolar)

Example: Insulation Material - Polyurethane
Specific Type - Pellethane 80A
Size - OD=.065", ID=.050"
Fabricator - Tubing Unlimited, Bethel, PA
Polymer Source - Acme Chemical

Conductor characteristics
Example: Conductor Characteristics
Material - Nickel-cobalt
Fabricator - Ace Wire
Alloy Source - WW Metals
Coil ID/OD - .025/.050"
No. of Filars - 5
Filar Diameter - .005"
Configuration - Bipolar coaxial

Description of electrode, including materials, type, etc. (eg., polished platinum alloy)

Connector type (eg., IS-1 Standard)

Standard lengths (eg., 52 cm, 60 cm)

II. Surveillance Protocol

A. Study Objectives:
The FDA will use the results of this study to determine and compare 5-year survival curves for leads from all sponsors. In order to accomplish this goal, all lead studies will be required to use a common set of definitions, basic statistical models, analytical methods, and minimum reporting requirements.

Therefore, the sponsor must design and implement a clinical study which yields statistically valid survival curves and actuarial life tables for each lead model group. For each lead model group implanted after January 1, 1982, the sponsor, using a life-table analysis, shall generate a pacemaker lead survival curve for each lead model group under study. At this time, the FDA is requiring that the duration of follow-up be, at a minimum, five years.

B. Definitions of Terms:
To ensure consistency in the determination of lead-related complications or failures and associated interventions or interactions, the FDA has provided the following list of definitions. The sponsor shall report any conditions that meet the criteria listed below for each lead model group under study. The sponsor who intends to use information contained in their postmarket performance files to satisfy some of the requirements for their postmarket surveillance study, must demonstrate conformance of the data submitted to these definitions. Refer to II.C.7 of the guidance for specific requirements for data analysis.

The sponsor shall provide the following algorithm and definitions of terms to clinicians as part of their study protocol:

Criteria for Lead-Related Complications and Failures:

WHEN: The following condition occurs:

- Conductor Failure
- Dislodgment
- Extracardiac Stimulation
- Insulation Breach
- Lead Impedance less than 200 ohms (describe how impedance was measured)
- Lead Impedance greater than 3000 ohms or beyond the measuring capabilities of the device (describe how impedance was measured)
- Loss of Capture
- Oversensing
- Perforation
- Undersensing/Loss of Sensing

AND: The condition was not:

- Caused by a pulse generator malfunction or
- Corrected by reprogramming of the pulse generator (except for reprogramming of mode or polarity)

THEN: The occurrence must be reported along with the following interventions/interactions in which the lead was:

- Abandoned Electrically
- Abandoned Surgically
- Modified Electrically
- Modified Surgically
- Removed/Explanted (full or partial)
- Tolerated (based on medical judgement)

DEFINITIONS OF TERMS

- Conductor Failure:

  Visual, electrical, and/or radiographic evidence of mechanical break within the lead conductor (includes connectors, coils and/or electrodes).

- Dislodgment:

  Radiographic, electrical or electrocardiographic evidence of electrode displacement from the original implant site or electrode displacement that adversely affects pacing and/or lead performance.

- Extracardiac Stimulation:

  Clinical observation of inadvertent muscle/nerve stimulation other than cardiac muscle where the pulse generator has been eliminated as a possible reason for the problem.

- Implanted Lead:

  A lead is considered implanted when the surgical incisions are closed.

- Insulation Breach:

  Visual, electrical, or radiographic evidence of a disruption or break in insulation.

- Lead Abandoned Electrically:

  A lead that remains connected to a pulse generator whose function is disabled through reprogramming (eg., changed from DDD to VVI) in response to a problem with the mechanical or electrical integrity of the lead.

- Lead Abandoned Surgically:

  A lead that is left in situ, with or without capping, detached from the pulse generator, and not used for sensing or pacing.

- Lead Modified Electrically:

  A lead that remains connected to a pulse generator whose function is altered through reprogramming (eg., changing from bipolar to unipolar) in response to a problem with the mechanical or electrical integrity of the lead.

- Lead Modified Surgically:

  Any mechanical alteration or repositioning of the lead (eg., replacing a connector).

- Loss of Capture:

  Intermittent or complete failure to stimulate cardiac depolarization at programmed settings delivered outside of the cardiac refractory period.

- Oversensing:

  At programmed settings, the inability to discriminate between extraneous signals, (eg., T waves, pacemaker stimuli, skeletal muscle potentials and extracardiac electromagnetic interference) and the intended cardiac depolarization.

- Perforation:

  Penetration of the lead tip through the myocardium, clinically suspected (microperforation), or confirmed by chest x-ray, fluoroscopy, echocardiogram, intracardiac electrogram, and/or visually.

- Removed/Explanted Lead:

  Any segment (partial) of a lead or whole lead system that is removed or explanted.

- Tolerated (Lead Function):

  When a physician determines that no corrective action is warranted to remedy a lead related complication or failure.

- Undersensing/Loss of Sensing:

  Intermittent or complete loss of sensing or failure to detect the intended intrinsic cardiac signals (atrial or ventricular) during pacemaker alert period at programmed settings.

C. Study Design:
For a lead model group which is no longer being implanted, patient enrollment in the study will be completely retrospective. For a lead model group which is currently being implanted, patient enrollment in the study may be retrospective and/or prospective. The sponsor may choose to do only a prospective study for a lead model group for which there will be a sufficient number of implants in the future. The sponsor may also choose to do an entirely retrospective study of a currently marketed lead model group, if adequate data for a sufficient number of implants is available. A combination of retrospective and prospective data may be necessary for some lead model groups. The approach used for each lead model group should be clearly identified (i.e., prospective, retrospective, both).

1. Description of the Study:
   The study may be composed of two parts, with a separate protocol prepared for each. One part will collect and analyze retrospective data while the other will collect and analyze prospective data. The data elements for both parts of the study should be the same, but there will be differences in the methods used to collect retrospective versus prospective data (eg., examination of medical records vs. proactive data collection). The prospective and retrospective parts of the study can be combined only if the two are determined to be sufficiently similar. In view of this, a completely retrospective or a completely prospective study will facilitate the analysis of the data.

2. Sample Size:
The sponsor shall assure that the study population is representative of the clinical experience for the entire target population. With a large number of participating centers, the sponsor will have difficulty maintaining compliance with the study protocol. Clearly a compromise is needed so that a sufficient number of investigators is included to obtain valid results without making the study so complex that data quality and uniformity suffer. As a challenging but manageable balance, a minimum of ten clinical centers should participate in the study. The FDA cautions that patient enrollment at a center should be accomplished by a method that minimizes bias. The protocol should explain how patients will be selected, and should include all patients implanted with the lead model group at an individual center unless the FDA approves some other sampling method.

In order to determine the sample size needed to obtain data to construct a statistically valid survival curve, the methods of Peto[1] and Dorey and Korn[2] may be used. The sample size needed at the end of the study is given by the equation

$$N = L^2(1-L)/s^2$$

where L is the expected fraction of leads surviving at the end of the study and s^2 is the estimated variance of L. The FDA recommends a precision of 3% with a 95% confidence level, which results in a value for s of

$$s = 0.03/1.645 = .01824$$

(where 1.645 is the 95th percentile of the standard normal distribution). To complete the calculation of sample size, the sponsor must estimate the expected rate of study dropouts and deaths. For the purposes of this discussion, the term "study dropouts" refers to patients other than those known to be dead for whom the sponsor is unable to collect data on the study variables. If X represents the fraction of patients who become study dropouts each year plus the fraction of patients who die each year, then the value of N obtained above must be adjusted using the equation

$$N/(1-X)^5 = \text{Initial Sample Size}$$

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[1]R. Peto et al., "Design and Analysis of Randomized Clinical Trials Requiring Prolonged Observation of Each Patient", British Journal of Cancer (1977) 35, 1-39.

[2]F.J. Dorey and E.L. Korn, "Effective Sample Sizes for Confidence Intervals for Survival Probabilities", Statistics in Medicine, (1987) vol 6, 679-687.

Within limits the study dropout rate may be controlled. A sponsor can choose to enroll fewer patients and tightly control the follow-up, or devote fewer resources to following each patient and enroll more patients initially. The FDA cautions that if the study dropout rate becomes too great, the study results may no longer be representative of the patient population. Therefore, the study dropout rate (not including deaths) over the entire 5-year study period should not exceed 20% of the initial population.

Serious consideration should be given to the assumptions used to calculate sample size because drastic deviations from these assumptions can lead to the need for adjustments during the course of the study so statistically valid results at the specified confidence level and precision are achieved.

3. Data Collection Plan and Forms:
   The sponsor shall provide copies of data collection forms and provide a plan for ensuring that complete data is collected for all patients enrolled in the study (either retrospectively or prospectively). Particular attention should be paid to collecting data that may be obtained by referring physicians rather than the participating clinical center.

4. Follow-up Plan:
   The sponsor shall develop a comprehensive plan for follow-up of patients to ensure that adequate lead performance data is collected at appropriate intervals.

5. Data Quality Control:
   A monitor shall be appointed by the sponsor to serve as an interface with the clinical sites and to assure data quality control. An auditing system should be implemented to ensure that accurate and complete data is obtained from all participating centers. Center visits should be conducted on a periodic basis to verify agreement between the medical records and the study forms. Assuming that the data will be entered into a computerized database, monitoring is also needed to ensure agreement between the study forms and the format used for the database.

6. Length of Study:
   At this time, the FDA believes that the duration of follow-up should be, at a minimum, five years. Therefore, the length of the study will be dependent upon the length of time taken for patient accrual. The FDA may determine, based on the findings provided in interim reports, that the length of the study may need to be adjusted.

7. Data Analysis:
   a. Any data submitted under these protocols which are represented to be numbers of leads, patients, implants, etc., shall be numbers actually determined from the study rather than numbers

which are estimates based on models or assumptions.

b. For each lead model group to be studied, the sponsor shall provide a life-table analysis and survival curve for the combined lead complications/failures as defined in Definitions of Terms (II.B). A tabular summary of the frequency of occurrence for each study complication/failure associated with an intervention/interaction shall also be provided. The sponsor shall collect and maintain data such that a life-table analysis for any of the individual study complications/failures or interventions/interactions can be provided to the FDA upon request.

c. Leads removed from service in anticipation of failure shall be considered to have failed.

d. Leads which are removed from service electively should not be designated as lead complications/failures if the removal is documented by the responsible medical practitioner to be for reasons other than one of the study complications/failures (eg., infection). These should be reported but censored in the analysis.

e. Leads that are dislodged and successfully repositioned shall not be considered lead complications/failures, however, the occurrences must be reported. Dislodged leads that are not successfully repositioned are considered lead complications/failures and must be reported and included in the analysis.

f. ***All deaths, regardless of cause, must be reported.*** The sponsor should actively encourage explantation of leads in the event of death, even when the lead is not suspected in the death.

g. In calculating life tables, the following conventions for handling cases of withdrawal and loss to follow-up shall be followed. The length of observation for withdrawals is the time from implant to the date of last contact. The length of observation for losses to follow-up is the time from implant to the time of loss if known. If the time of loss is not known, then it should be considered as the midpoint of the interval between the time of the report of loss and the time of the last documented follow-up. A study patient is considered lost to follow-up only after repeated attempts, for up to one year, to locate him have been unsuccessful. Numbers of patients who are considered lost to follow-up or withdrawn should be reported in separate columns of the life table.

h. In the interest of uniformity of life-table analyses among sponsors, an interval of 3 months should be used.

D. Reporting Plan:

1. The sponsor shall provide the FDA with written notification of the initiation of the study. The sponsor shall analyze the data collected and provide the cumulative results (as discussed in Data Analysis (II.C.7)) for each lead model group being studied in reports to the FDA at six and 12 months after approval of the protocol. Thereafter, reporting shall be done annually. This information shall include, but not be limited to, for each lead

model group, the number of leads implanted to date (by calendar year) since first implantation and the total number of patients with functioning leads remaining at the close of the current reporting period.

2. In addition to the results of the clinical studies, each interim and final report shall provide a cumulative summary report of the analyses of all explanted leads, regardless of source, giving a table of the frequency of occurrence of each failure mode for the subject lead model groups at the end of each reporting period.

3. Each interim and final report shall provide a cumulative summary report of all deaths, regardless of cause.

At the conclusion of the study of a particular lead model group, a final report shall be prepared and submitted to the FDA. The FDA will then determine whether the requirements under section 522 have been satisfied for that lead model group or whether further safety and effectiveness data are required.

If a sponsor, using his own criteria, determines that a lead model group is failing at an unacceptable level, the normal obligation to report immediately to the FDA shall apply, rather than waiting for the next DPS interim or final report.

III. Principal Investigator

The sponsor must document the experience and qualifications and disclose any financial ties to the sponsor of all major scientific contributors to the study. This requirement applies not only to the principal investigator, who may be a company employee, but also to the primary investigator at each clinical center. This information is similar to that required for government funded research grant proposals and must include:

A. A discussion of the pertinent qualifications and experience of the individual
B. Curriculum Vitae
C. Investigator Agreement
D. Disclosure of financial interests in companies which manufacture pacemaker leads or pacemakers

IV. Informed Consent and Institutional Review Board Considerations

The sponsor shall ensure that the protocol complies with the requirements of 21CFR50 and 21CFR56 concerning informed consent and IRB approval.

V. Attachments

A. Methodology for analyzing lead-related complications/failures:
The sponsor shall provide copies of both the current methodology and the proposed methodology for analysis of lead complications/failures.This methodology should identify the steps and decision points used to determine the type and mode of failure for leads that remain implanted.

B. Methodology for explanted lead analysis:
The sponsor shall provide copies of both the current and proposed methodologies for the analysis of explanted leads. This methodology should include any instructions for explanting and handling the lead prior to analysis and the test procedures used. This section should also identify the sites involved in the analysis (eg., clinical center biomedical engineering lab, sponsor, independent testing facility, etc.)

C. Methodology for statistical analysis:
The sponsor shall provide a complete description of the statistical methods to be used in the analysis of pacemaker lead survival.

D. List of leads for which exemptions have been granted or are pending:
The sponsor shall provide, in tabular form, a list of leads or lead model groups for which the FDA has granted exemption from this DPS study, with the date of the letter granting exemption. The sponsor shall also provide a list of leads or lead model groups for which the sponsor has requested exemption, along with the date of the request to the FDA.

E. List of leads which you manufacture or market, but for which you do not have primary responsibility as specified in "Introduction":
The sponsor shall provide, in tabular form, a list of leads or lead model groups for which another firm has primary responsibility. This list must identify, for each lead or lead model group, the PMA or 510(k) holder.

ATTACHMENT 1
Format for Reporting Information Required in Section I.D
(Device Description)

DESIGNATION OF LEAD MODEL GROUP:

TYPE OF LEAD:

RANGE OF AVAILABLE CATHETER LENGTHS:

TYPE OF ELECTRODE FIXATION (attach diagram):
Description:

LEAD INSULATION MATERIAL (general & specific):

DESCRIPTION OF CONDUCTOR CHARACTERISTICS (including materials, fabricator, etc.):

DESCRIPTION OF ELECTRODE (including materials, type, etc.):

LIST OF CONNECTOR TYPES:

LIST OF LEAD MODELS INCLUDED IN GROUP:

LIST OF ASSOCIATED PMA OR 510(k) NUMBERS: