This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP's.

IMPLANTABLE PACEMAKER TESTING GUIDANCE

by Donald F. Dahms

This guideline describes a general framework for design verification testing of a safe and effective implantable cardiac pulse generator. The tests are designed to reasonably assure safe and effective functioning of the pacemaker in the patient, according to written specifications of performance, and its survival under expected environmental conditions in the body and during storage, shipping and handling.

This guideline is intended to apply to bradycardia pacemakers which are to be commercially marketed and are manufactured using standard production techniques and methods. It may not apply to devices which are used in limited research applications. Major variations from these guidelines may be warranted in some cases such as the latter. Some devices may be qualified in whole or in part by similarity to previously qualified ones. In all cases arguments for any variations must be made based on the nature of the mission of the device and on any claimed similarities.

The testing is that referred to in the premarket approval regulation 21 CFR Part 814 and must be reported as described in 21 CFR Part 814 articles 814.20(b)(3)(v) and 814.2020(b)(6). The testing requirements include any and all additional requirements imposed or referred to in the "Good Manufacturing Practice for Medical Devices: General" Regulation (21 CFR Part 820). This guideline represents practices which have been developed over several years and are generally understood by the pacemaker industry.

The tests are grouped into (A) <u>in vitro</u> component tests, (B) <u>in vitro</u> device tests, (C) animal tests, (D) biocompatibility tests, (E) clinical investigation and (F) Manufacturing. An appendix provides a sample protocol for preclinical pacemaker testing.

A. <u>In Vitro</u> Component Tests:
Component parts shall be tested for design verification by the pulse generator manufacturer of its supplier according to written specifications of performance and testing (such as Military Standards or their equivalent).

The component parts referred to shall include, but not be limited to:

Hybrid Integrated Circuit and/or Chip Carrier
Battery
Connector
Other components where necessary to assure reliable operation

The verification testing shall be appropriate for the component and shall include appropriate operational environmental, and reliability tests with tolerances and limits compatible with the entire system's specifications.

B. In Vitro Finished Device Testing:

Pulse Generators

Pulse generators built for verification testing shall be representative of the marketable product in terms of components and manufacturing processes used. When completed (usually by the time of application for premarket approval), tests should be performed on devices manufactured from qualified components using validated processes. Where appropriate, tests should be performed on in-specification devices which have been subjected to all applicable post-process techniques (e.g. cleaning, sterilization and finishing).

The following testing shall be performed:

Electrical Characterization

This testing shall be designed to verify the proper functioning of the pulse generator within specified tolerances in the human body during the device's expected operational life. All parameters such as rate, pulse amplitude, pulse width, sensitivity, and timing cycles and periods; and all features such as intracardiac electrograms, remote measurements, hysteresis, rate fallback, and elective replacement indicators, must be characterized for functioning under expected temperatures (30C to 40C), loads (300 ohms to 2000 ohms), and battery voltage's beginning of life (BOL) to end of service (EOS). The device shall be programmed to each mode and feature and to the lowest, nominal and highest values of programmed parameters. Analysis of the effects of worst case combinations of load, temperature and battery voltage must be made.

Environmental

The pulse generator shall be subjected to a sequence of mechanical, and environmental tests to assure that the device will meet its labeled specifications after being subjected to conditions that exceed those normally seen in handling, shipping, storage or clinical use. Test shall include:

Temperature storage or cycling
Mechanical vibration
Mechanical shock

Interference

The pacemaker shall be evaluated for effects on its functioning and/or programming by external sources of interference. Sources of interference can be from the general environment, in the clinical setting, occupational environments, or from the human anatomy. These may include, as appropriate to the device design, electromagnetic, electrical, magnetic, mechanical, thermal, acoustic, or chemical interference. The effects of interference on such features as sensing, device algorithms, rate responsive sensors shall be characterized. The following sources of interference shall be evaluated for all devices as appropriate to the specific device design:

- o Conducted and Radiated Electromagnetic Interference
- o Electrosurgical Units
- o Defibrillation

The results must be analyzed to assure that the pulse generator meets specifications and device labeling.

Reliability

The device must be tested and analyzed from a reliability standpoint. Testing of the device or, where appropriate, its components, must include accelerated life testing which will demonstrate the expected real time longevity performance and failure rate of the device. An analysis of the results of this testing and/or data from the literature shall result in a predicted failure rate of the device.

Programmer

Programmers built for verification testing shall be representative of marketable products and subjected to functional, environmental, interference, software and reliability testing. This testing must be designed to assure its operation according to written specifications in conjunction with any and all of its intended pulse generators, under specified, expected environmental conditions; and its survival in use as well as in storage, shipping and handling.

C. Animal Testing:

Animal testing should be performed where appropriate to verify functions, features or other characteristics of the device.

D. Biocompatibility Testing:

For a material which has been tested and used previously in direct blood contacting devices, a sponsor may submit information available in publications or other legitimate sources which show that the material is nontoxic in tests identical or equivalent to those listed below.

All new materials in the non-hermetic portion of the pulse generator must pass the tests below to insure safety for use in permanent implant.

The effects of sterilization on device materials and potential leachables, as well as toxic by-products resulting from sterilization, should be considered. Therefore, testing should be performed on the sterilized final product or representative samples therefrom. Specific chemical analyses of the sterilized final product and any leachable material from the final sterilized product must be performed before toxicity testing. The chemical analyses must be submitted together with toxicity data to FDA for review. The analyses and tests for leachable materials must be conducted by choosing appropriate solvent systems which will yield a proper extraction of the leachables. Extraction temperature should be 50°C which is one of the three temperatures recommended in U.S.P. XXI. The required toxicity tests for implantable devices are listed as follows:

1. United States Pharmacopea:

(U.S.P.) XXI (Class V) Biological Tests for plastics and U.S.P. XXI Intramuscular implant tests and U.S.P. XXI pyrogen tests.

2. Sensitization assay:

Estimate the potential for sensitization of a material by using a test such as the guinea pig maximization test.

3. Cytotoxicity test:

Determine the lysis of cells (cell death), the inhibition of cell growth, and other toxic effects on cells caused by materials and extracts from the materials using cell culture techniques.

4. Hemolysis:

Determine the degree of red cell lysis and the separation of hemoglobin caused by materials in-vitro. Describe the test methodology.

E. Clinical Investigation:

Objectives

The objective of the study must be defined such that the study will constitute a demonstration of reasonable assurance of the safety and efficacy for the device. The study must establish a list of indications and contraindications and, if any, warnings and precautions for the use of the device. Generally, pacemakers must show pacing and sensing capabilities with modes, parameters, features and logical combinations of these shown to be safe and effective within the meaning of the Federal Food, Drug and Cosmetic Act, as amended, 1980.

Patient Selection

Patients should be selected for the clinical studies who can be expected to benefit from the device's capabilities and whose conditions can demonstrate its effectiveness. The patient should be psychologically stable, cooperative and available for follow-up and have a reasonable life expectancy so that a proper clinical evaluation of the device might conducted.

Investigators

Investigators for pacemaker studies should be selected who are qualified by training or experience in cardiovascular diseases at a minimum. In the case of devices with special features, trained physicians with special skills, should be specified in a representative sample of the investigators.

Design of the Study

I The investigational protocol should be clear, simple and shall include all pre and post implantation testing and include procedures for follow-up. The protocol must show how the data from the study will be organized in a manner which will clearly fulfill each of the specific study objectives, including the reasonable assurance of safety and effectiveness.

II Sensor driven pacemakers must show that the paced rate changes appropriately in response to the sensor signal. The study design will include an identification of potential patients in whom the use of the specified sensor(s) and/or rate pacing is contraindicated so that this information can be included in product labeling. Provisions for treadmill testing, sensor on/off testing shall be included.

III Modes or features which are commonly used or whose efficacy has been previously evaluated in comparable devices may only require limited evaluation or simply demonstration to establish their efficacy. New sensing or therapeutic modes technical advances, require more extensive study and effort to prove safety and efficacy.

Study Dimensions

The dimensions of a clinical study are the numbers of devices, investigators, durations of phases and approval requirements are listed below in a table. The choice of regular or "NASPE" type study or any other options must be stated in the protocol.

The minimum requirements dimensionally for a clinical study for the filing of a pacemaker approval application is as follows.

Regular:

The submission of data and its performance evaluation on 100 devices implanted for a minimum of 120 days each;

Modified NASPE:

The submission of data on 30 devices each intensively studied for 30 days and implanted for a minimum of 90 days and an additional 70 devices each implanted for a minimum of 30 days. At least ten investigators must have had a hands on study of at least three devices.

Table of Clinical Dimensions

REGULAR	Phase I	Phase II	Phase III	Phase IV
Number of Devices	50	250	500	1000
Number of Investigators	10	50	100	200

NOTES:

Monthly Reports to FDA are required during Phase I of the study.

For regular studies FDA Approval must be granted to proceed to Phase II through an IDE Supplement containing the performance evaluation of 30 devices with a mean experience of 30 days.

For Modified NASPE Studies - After 30 devices have been implanted and intensively studied for a minimum of 30 days the investigators must be given data on all implants and agree that the study may proceed into the next phase based upon evaluation of this data with regard to safety and effectiveness. The results of this meeting must be reported to FDA in an IDE supplement.

FDA Approval must be granted to proceed to Phase III based upon the fulfillment of the minimum filing requirements for a premarket approval.

FDA approval must be granted to proceed to Phase IV based upon the results of the Cardiovascular Devices Panel review.

Programmers

Programmers must be shown to be capable of successfully and accurately changing parameters in the pulse generator and of performing all other designed features, such as telemetry reception, by medical personnel in a clinical environment.

Follow-up

Follow-ups at predischarge, 1 month, 3 months, 6 months, 12 months and every 6 months thereafter until FDA approves a PMA application should be scheduled. Any safety or effectiveness issues should be studied. Follow-up data gathered during the follow-up portion of the study. Patient diaries should be used for recording symptoms or other events when this would enhance the objectives of the study. Explant forms should be used to record data concerning the explant including any circumstances and reasons.

Records Requirements:

The following data as a minimum must be recorded and reported. Much of this data should be included on implantation, follow-up and explanation forms. Any comparisons of data between devices, groups, or controls or any therapeutic success versus failure data must be analyzed when appropriate using sound statistical methods.

Description:

The patient population must be described with such factors as age, sex, indications, associated conditions, symptoms, concomitant drug therapy and duration of implant included. There must be a list of investigators and institutions and quantities implanted by them.

Implantation:

The following data is required:

- Electrodes used - description and model number
- Initial or replacement generator
- Technical data - thresholds, amplitudes, impedances
- Programmed parameters
- Telemetered data
- Results of special tests such as tachyarrhythmia induction and termination.

Follow-up:

o Reprogramming of parameters
o A summarized explanation of all adverse experiences, complications, and observations
o All changes in patients conditions such as symptoms, drug therapy, arrhythmias, and exercise duration
o An explanation of all explants including device failures and corrective measures, deaths - The circumstances of all deaths must be explained as completely as possible and device relatedness must be addressed
o Adherence to follow-up schedule which will include the percent of follow-ups being met by each investigator
o Quantities of successes and failures of anti-tachyarrhythmia devices with a breakdown of data relative to age, sex, indications etc.
o The results of special studies such as retrograde conduction, postural effects, arrhythmia control, holter monitoring exercise testing or special programmings.

F. Manufacturing

A description of the testing during the manufacturing process must be included in the PMA Application in the section required by 21 CFR 814.20(b)4(v). This testing should complement the design verification testing to ensure that each manufactured unit will operate within the specifications of the design with respect to tolerances, environmental considerations, and interfaces. Summary descriptions of the following tests should be included:

Tests
Component
Screen
Burn-in
Assembly
Final Product
Special QC
Requalification

A specification control drawing for the pulse generator must be included with the QC tests which ensure the testing of selected parameters noted.

FOR MORE INFORMATION CONTACT:
DIVISION OF SMALL MANUFACTURERS ASSIST.
MAIN 301-443-6597
800-638-2041
FAX 301-443-8818