



PMS

P950001

Memorandum

Date **MAY - 8 1996**

From Director, Office of Device Evaluation (HFZ-400)
Center for Devices and Radiological Health (CDRH)

Subject Premarket Approval of Guidant Corporation
SELUTE® Steroid Eluting Endocardial Lead Models 4185 and 4285 -
ACTION

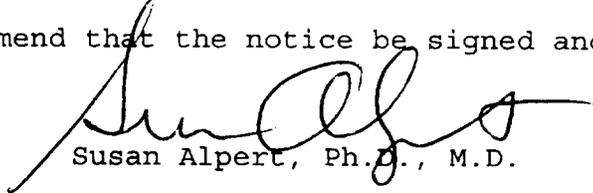
To The Director, CDRH
ORA _____

ISSUE. Publication of a notice announcing approval of the subject PMA.

FACTS. Tab A contains a FEDERAL REGISTER notice announcing:

- (1) a premarket approval order for the above referenced medical device (Tab B); and
- (2) the availability of a summary of safety and effectiveness data for the device (Tab C).

RECOMMENDATION. I recommend that the notice be signed and published.


Susan Alpert, Ph.D., M.D.

Attachments
Tab A - Notice
Tab B - Order
Tab C - S & E Summary

DECISION

Approved _____ Disapproved _____ Date _____

Prepared by PREPARED BY Lynette Gabriel, CDRH, HFZ-450, 4/24/96, 443-8243

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

[DOCKET NO. _____]

GUIDANT CORPORATION; PREMARKET APPROVAL OF SELUTE® STEROID
ELUTING ENDOCARDIAL LEAD MODELS 4185 AND 4285

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application by Guidant Corporation, St. Paul, MN, for premarket approval, under section 515 of the Federal Food, Drug, and Cosmetic Act (the act), of SELUTE® Steroid Eluting Endocardial Lead Models 4185 and 4285. FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter on MAY - 8 1996, of the approval of the application. In addition, the SELUTE® Steroid Eluting Endocardial Lead Models 4185 and 4285 requires tracking under section 519(e) of the act as amended by the Safe Medical Devices Act of 1990.

DATE: Petitions for administrative review by (insert date 30 days after date of publication in the FEDERAL REGISTER).

ADDRESS: Written requests for copies of the summary of safety and effectiveness data and petitions for administrative review, to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 1-23, 12420 Parklawn Drive, Rockville, MD

20857.

FOR FURTHER INFORMATION CONTACT:

Lynette Gabriel

Center for Devices and Radiological Health (HFZ-450)

Food and Drug Administration

9200 Corporate Blvd.

Rockville, MD 20850

301-443-8243.

SUPPLEMENTARY INFORMATION: On January 13, 1995, Guidant Corporation, Inc., St. Paul, MN, 55112-5798 submitted to CDRH an application for premarket approval of SELUTE® Steroid Eluting Endocardial Lead Models 4185 and 4285. The device is a permanent pacing lead and is indicated for chronic pacing and sensing of the ventricle when used with a compatible pulse generator.

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory panel, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

On MAY - 8 1996, CDRH approved the application by a letter to the applicant from the Director of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which CDRH based its approval is on file in the Dockets Management Branch (address above) and is available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

OPPORTUNITY FOR ADMINISTRATIVE REVIEW

Section 515(d)(3) of the act (21 U.S.C. 360e(d)(3)) authorizes any interested person to petition, under section 515(g) of the act (21 U.S.C. 360e(g)), for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under part 12 (21 CFR part 12) of FDA's administrative practices and procedures regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under 10.33(b) (21 CFR 10.33(b)). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 515(d), 520(h), (21 U.S.C. 360e(d), 360j(h)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated: _____.



Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Ms. Sheryl A. Poganski
Senior Regulatory Affairs Associate
Guidant Corporation
4100 Hamline Avenue North
St. Paul, Minnesota 55112-5798

MAY 8 1996

Re: P950001
SELUTE® Steroid Eluting Endocardial Lead Models 4185 and 4285
Filed: January 13, 1995
Amended: November 8, 1995, December 21, 1995,
January 31, 1996, and March 7, 1996

Dear Ms. Poganski:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the SELUTE® Steroid Eluting Endocardial Lead Models 4185 and 4285. This device is indicated for chronic pacing and sensing of the ventricle when used with a compatible pulse generator. We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed

Page 2 - Ms. Sheryl A. Poganski

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

In addition under section 522(a) of the act manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under section 522(a)(1)(A) the above noted device as requiring postmarket surveillance.

Upon approval and within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you will be required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

At that time you should submit five (5) copies to:

Postmarket Studies Document Center
1350 Piccard Drive (HFZ-544)
Rockville, Maryland 20850

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will be considered violations of section 522.

In accordance with the Medical Device Amendments of 1992, failure of a manufacturer to meet its obligations under section 522 is a prohibited act under section 301(q)(1)(C) of the Federal Food, Drug and Cosmetic Act (the act) (21 U.S.C. 331(q)(1)(C)). Further, under section 502(t)(3) of the act (21 U.S.C. 352(t)(3)), a device is misbranded if there is a failure or refusal to comply with any requirement under section 522 of the act. Violations of sections 301 or 502 may lead to regulatory actions including seizure of your product, injunction, prosecution, or civil money penalties or other FDA enforcement actions including (but not limited to) withdrawal of your PMA.

Page 3 - Ms. Sheryl A. Poganski

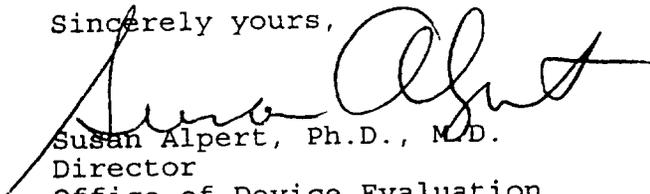
If you have any questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch, at (301) 594-0639.

Under section 519(e) of the act (as amended by the Safe Medical Devices Act in 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of device user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. Under section 519(e), FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonably likely to have serious adverse consequences.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR § 821.20(b) and the devices that FDA has designated for tracking at 21 CFR § 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705-10709 (March 27, 1991), 57 FR 22973-22975 (May 29, 1992), and 58 FR 43451-43455 (August 16, 1993)).

If you have any questions concerning this approval order, please contact Lynette Gabriel at (301) 443-8243.

Sincerely yours,



Susan Alpert, Ph.D., M.D.

Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

Summary of Safety and Effectiveness

I. GENERAL INFORMATION

Device Generic Name: Transvenous Unipolar/Bipolar Pacing Lead

Device Trade Names: SELUTE®, Steroid Eluting Endocardial Lead
Models 4185 and 4285

Applicant's Name
and Address: Guidant Corporation Cardiac Pacemakers (CPI)
4100 Hamline Ave. North
St. Paul, MN 55112-5798

PMA Number: P950001

Date of Notice of Approval
to Applicant: May 8, 1996

II. DEVICE DESCRIPTION

The SELUTE® Steroid Eluting Endocardial Lead, Models 4185 and 4285 are steroid-eluting, tined, ventricular transvenous unipolar and bipolar pacemaker leads designed for use as an integral part of a pacemaker system with IS-1 ports. IS-1 refers to the draft international standard ISO 5841-3:1992(E). The lead uses a platinum-iridium porous-tip electrode that provides an efficient pacing and sensing surface by promoting fibrotic tissue ingrowth and physically stabilizing the tissue interface.

III. INDICATIONS FOR USE

The SELUTE® Steroid Eluting Endocardial Lead, Models 4185 and 4285 (SELUTE) are intended for chronic pacing and sensing of the ventricle when used with a compatible pulse generator.

V. CONTRAINDICATIONS

- Use of this lead is contraindicated in patients with a hypersensitivity to a single dose of 1.0 mg of dexamethasone sodium phosphate.
- When tricuspid valvular disease is present, use of a transvenous ventricular lead is contraindicated
- The use of an endocardial ventricular lead is contraindicated in patients with mechanical tricuspid heart valves.

VI. WARNINGS

- The use of battery-powered equipment is recommended during lead implantation and testing to protect against fibrillation that may be caused by alternating currents.
- Line-powered equipment used in the vicinity of the patient must be properly grounded.
- Lead connector pins must be insulated from any leakage currents that may arise from line-powered equipment.

VI. PRECAUTIONS

General

- The SELUTE lead and its accessories are intended for one-time use only. Do not reuse.
- Do not use unipolar leads having 3.2-mm connectors with pulse generators programmed to the bipolar mode. No output will result.
- Prior to the implantation of this lead, confirm lead/pulse generator compatibility with CPI technical services.

- It has not been determined whether the warnings, precautions, or complications usually associated with injectable dexamethasone sodium phosphate apply to the use of the low concentration, high-localized, controlled-released device. For a listing of potentially adverse effects, refer to the Physicians' Desk Reference.
- Defibrillating equipment should be kept nearby for immediate use during the implantation procedure.

Handling

- Do not use the vein pick to puncture the vein or dissect tissue.
- Do not wipe or immerse the electrode in fluid. Such treatment will reduce the amount of steroid available when the lead is implanted.
- Do not allow the electrode surface to come in contact with surface contaminants.
- Do not use excessive force or surgical instruments in handling to prevent damage to lead or potential lead dislodgment. Use an anchoring sleeve to avoid placing the lead under extreme tension.
- Chronic repositioning may adversely affect the lead's low-threshold performance because the steroid may be depleted.
- Do not apply pressure to the electrode tip.
- Lead conductor insulation material is silicone rubber, which tends to attract particulate matter and must be protected from surface contamination before implantation.
- Avoid bending the coil conductor, since attempts to restore the original shape may weaken the structure. Although pliable, a lead is designed to tolerate only normal flexing.

Implanting

- Do not bend the SELUTE lead with the stylet in place because it may damage the conductor and insulating material.
- When attempting to implant the lead via a subclavian puncture, do not insert the lead under the medial one-third region of the clavicle. Damage to the lead is possible if the lead is implanted in this manner. If implantation via the subclavian vein is desired, the lead must

enter the subclavian vein near the lateral border of the first rib and must avoid penetrating the subclavius muscle. It is important to observe these implant precautions in order to avoid clavicle/first rib damage to the lead. It has been established in the literature that lead fracture can be caused by lead entrapment in such soft tissue structures as the subclavius muscle, costocoracoid ligament, or the costoclavicular ligament. Excessive lead compression has also been reported in patients with anatomical abnormalities between the clavicle and first rib.

- When implanting the lead via a subclavian puncture, allow slack in the lead between the distal lead stabilizer and the venous entry site. This will help minimize flexing at the stabilizer and interaction with the clavicle/first rib region.

Electrical Performance

- When ligating the vein, avoid too tight a stricture. A tight stricture may damage the silicone rubber insulation or sever the vein.
- Avoid dislodging the electrode tip during the anchoring procedure.
- Remove the stylet and the stylet guide before connecting the lead to the pulse generator. Under no circumstances should the stylet be left in the lead. Leaving the stylet in the lead may cause (1) lead perforation, (2) myocardial perforation, or (3) inability to remove the stylet and reposition the lead.
- Do not remove or cut the suture sleeve from the lead because either action may damage the lead.

VII. ADVERSE EVENTS

A total of five complications and 11 observations were reported during the clinical investigation, which involved 178 SELUTE patients and 3076 cumulative implant months (mean implant duration 17.3 months). Twelve patients died during the course of the clinical study; none of the deaths were judged to be device-related. Table 1 reports complications and observations from the SELUTE clinical investigation.

Table 1. SELUTE Clinical Investigation Complications and Observations

	# of pts (n=178)	% of pts	# of leads (n=178)	% of leads	# of AEs ¹
Complications (total)	5	2.81%	5	2.81%	5
Lead dislodgment, post-implant	2	1.12%	2	1.12%	2
Infection (procedure-related)	1	0.56%	1	0.56%	1
Pneumothorax (procedure-related)	1	0.56%	1	0.56%	1
Placement difficulty (anatomical)	1	0.56%	1	0.56%	1
Observations (total)	10	5.62%	10	5.62%	11
Infection (procedure-related)	2	1.12%	2	1.12%	2
Thrombosis (procedure-related)	1	0.56%	1	0.56%	1
Difficulty positioning lead	2	1.12%	2	1.12%	2
Elevated threshold at implant	1	0.56%	1	0.56%	1
Excessive change in impedance	1	0.56%	1	0.56%	1
Loss of capture	1	0.56%	1	0.56%	1
T-wave oversensing	1	0.56%	1	0.56%	2
Undersensing	1	0.56%	1	0.56%	1

1. AE = Adverse Event defined as total (lead and non-lead related) number of complications and observations
2. Complications were defined as adverse events requiring invasive measures to correct (e.g., surgical intervention).
3. Observations were defined as adverse events that were correctable by noninvasive measures (e.g., reprogramming).

Historically reported potential physical effects from implantation of a lead are listed below:

- Cardiac perforation
- Myocardial injury
- Lead fracture, insulation break
- Venous perforation
- Displacement/dislodgment
- Infection
- Transvenous lead-related thrombosis
- Threshold elevation
- Pneumothorax

- Air embolism
- Venous occlusion
- Erosion/extrusion
- Incomplete connection with pulse generator
- Myocardial irritability
- Bleeding
- Hematoma
- Local tissue reaction
- Allergic reaction
- Fibrotic tissue formation
- Keloid formation

VIII. ALTERNATIVE PRACTICES AND PROCEDURES

Electrical pacing of the heart with a cardiac pulse generator and transvenous steroid eluting leads is the standard and accepted treatment modality for the indications described above. Other commercially available leads may meet the needs of the patients with the symptoms described above.

IX. MARKETING HISTORY

As of October 26, 1995, approximately 7300 SELUTE Models 4185/4285 Steroid Eluting Porous Tip Ventricular Leads have been sold worldwide including the following countries: Japan, Austria, Belgium, France, United Kingdom, Germany, Holland, Greece, Turkey, Sweden, Denmark and Finland.

X. SUMMARY OF STUDIES

Nonclinical laboratory (bench) tests were performed to evaluate the mechanical and electrical integrity of the SELUTE Lead. These tests revealed that the leads met the requirements of the device specifications.

A. Component Tests

- SELUTE Lead subassembly tests included the electrode portion of the lead which is slightly different from other CPI bradycardia leads because of the steroid carrier (drug plug) in the electrode. Mechanical pull tests and drug plug analyses were conducted. The remaining portions of the lead, for example, lead body and connector, are comparable to CPI market-released Models 4161 (unipolar)/4261 (bipolar). All parts tested passed the test acceptance criteria.
- Testing performed on full lead assemblies examined aesthetic quality, mechanical integrity, electrical integrity, and appropriate dimensions (length). Samples were tested to verify that the leads met product specifications. All samples met the test acceptance criteria.
- Fatigue resistance of the conductor coils was evaluated through *in vitro* flex testing in a dry environment. Two (2) mid-sections and a distal section of each lead were evaluated to verify that they could withstand flex stress. In accordance with the test protocol and acceptance criteria, all lead segments withstood flex cycling without failure of the conduction path. The lead segments met the post-flex resistance acceptance criteria of remaining within 10% of the initial (pre-flex) resistance.

Additional flex fatigue testing was conducted in a wet environment. Again, the lead segments met the post-flex resistance acceptance criteria of remaining within 10% of the initial (pre-flex) resistance.

- Connector performance testing was conducted. The tests included dimensional analysis, insertion and withdrawal force testing, setscrew deformation testing and lead connector electrical isolation testing. All connectors passed the dimensional and functional requirements.

B. In-Vitro (Bench) Tests

Bench tests were performed to evaluate the mechanical and electrical integrity of the SELUTE Lead. Bench tests included Product Evaluation Testing, Process Validation Testing, Flex Fatigue Testing, IS-1 Connector Testing and Thermal/Humidity Resistance Testing. These tests revealed that the leads met the requirements of the device specifications.

1. Product Evaluation

Product Evaluation Testing was performed to evaluate the mechanical and electrical integrity of the SELUTE Lead.

- ELECTRODE TIP SUBASSEMBLY PULL TESTS: Pull testing performed on electrode tip subassemblies examined the bond/crimp strengths of various joints. Samples of each subassembly type were pull tested using a tensile testing machine. The samples were pulled until separation occurred. The connections tested were:

Tip Electrode/Conductor Coil Crimp Strength: The crimp between the tip electrode and the conductor coil was tested on eleven subassemblies. All samples passed the acceptance criterion of not less than 2.20 lb.

Tine Molding/Insulation Tubing Bond Strength: The bond between the molded tine neck and the insulation tubing was tested on ten subassemblies. All samples passed the acceptance criterion of not less than 0.50 lb.

Tine Molding/Tip Bond Strength: The bond between the molded tine neck and the tip subassembly was tested on ten samples. All samples passed acceptance criterion of not less than 1.10 lb.

- FULL LEAD ASSEMBLY TESTS: Manufactured leads were subjected to the following evaluations to assure that completed assemblies functioned per design intent:

Resistance Test: The direct current resistance was measured on 12 completed leads to assess continuity of the crimp and weld joints, and to measure the overall resistance of the lead. All leads met the acceptance criteria of 100 ± 10 ohms for the bipolar lead cathode circuit path (Tips), 50 ± 5 ohms for the bipolar lead anode circuit path (anode) and 45 ± 5 ohms for the unipolar model cathode circuit path.

Stylet Insertion/Withdrawal Performance : Forces required to insert and withdraw stylets into and out of fully assembled leads were measured. A 0.016" diameter tapered stylet was inserted and withdrawn from each lead while the lead was straight. All 12 leads passed the acceptance criterion of not requiring more than 4.0 oz. of force for insertion or withdrawal.

Axial Pull Test: Following stylet insertion/withdrawal testing, the same 12 leads were subjected to an axial pull test where a 1.1 lb weight was applied for up to 60 minutes, at which time the lead length was measured. After 60 minutes, the lead length was measured again. All specimens passed the acceptance criterion of no permanent deformation in excess of 5%.

Insulation Dielectric Strength: Insulation dielectric strength for the sensing/pacing cathode conduction path and the sensing/pacing anode conduction path was assessed

on the 12 leads that were subjected to the axial pull test. All assemblies passed the acceptance criterion of no current above 0.6 milliamps when 1500 VAC were applied between adjacent conductors.

Drug Plug Analysis: The quantity of dexamethasone sodium phosphate (DSP) was measured in ten steroid carriers, tip assemblies via an ultraviolet (UV) spectrophotometer. This measurement was made to verify appropriate steroid quantity. The drug plugs were within the design acceptance criteria of 0.45 - 0.95 mg of DSP.

- PACKAGED LEAD TESTS: Packaged leads were subjected to the following evaluations to assure that the leads met the requirements of the device specifications. The packaging tests included a visual inspection, an ASTM shipping test, x-ray, Tyvek peel tests, lead visual inspection and lead dimensional analysis.

Packaging Visual: Twelve packages were visually inspected per the final packaging drawings. Packages must have proper labeling, correct literature, proper assembly and not show any external damage. All samples passed the acceptance criteria.

ASTM Shipping Test and X-ray Inspection: The ASTM shipping test D-4169 was performed on 12 final packaged leads by an outside testing facility. Following testing, the packages were required to be in good condition, although slight damage to the corners and edges were acceptable. Leads were to retain their proper orientation with no damage. All samples passed the visual and X-ray inspection with no discrepancies noted.

Tyvek Peel Test: Peel testing of 12 heat sealed Tyvek tray covers was conducted to verify a minimum (1.0 lb) and maximum (2.5 lb) peel strength requirement. In performing the test, a one inch wide strip of the Tyvek cover was peeled across the tray seal at a rate of ten inches per minute using an Instron pull tester. The peel tests passed the requirements with a pull force ranging from 1.5 to 2.5 lbs.

Visual Inspection and Dimensional Characteristics: Visual inspection of 12 finished leads for surface imperfections and proper assembly demonstrated that all leads met the requirements of the device specification. No discrepancies were noted. Dimensional analysis of these same leads at seven locations with an optical comparator verified that the leads met assembly drawings.

All subassemblies and full lead assemblies that underwent Product Evaluation Testing passed the test acceptance criteria.

2. Process Validation Testing

Testing was conducted to validate the ability of the manufacturing process to produce SELUTE leads meeting product specifications. Lead subassemblies and full lead assemblies were evaluated.

- LEAD SUBASSEMBLIES (MANUFACTURING PROCESS TESTING): Pull testing performed on lead subassemblies examined the bond/crimp strengths of various joints. Samples of each subassembly type were clamped in a test fixture and pulled or pushed until separation occurred. Lower tolerance limits at a 95% probability were reported for all bonds and crimps measured. Testing of the drug carrier verified the appropriate concentration of Dexamethasone Sodium Phosphate (DSP). All samples met the test acceptance criteria. These results are summarized below.

Electrode Screen to Electrode Collar Bond Strength: The bond strength of the sintered electrode screen to the electrode collar was tested via a push test on fifteen subassemblies. All samples passed the acceptance criterion of not less than 2.20 lb.

Neck Tine Strength: For thirty-two samples, the strength of the tines on the molded necks was measured by pull testing. All samples passed the acceptance criterion of not less than 0.50 lb.

Mass of DSP in Drug Carrier: A UV spectrophotometer was used to determine the mass of DSP in fifteen manufactured carriers. The drug was eluted from the carriers in distilled water and then measured by UV absorbency. All samples passed the acceptance criterion of not less than 0.45 mg and not greater than 0.95 mg.

Electrode to Base Crimp Strength: The strength of the electrode to base crimp strength was pull tested on fifteen samples. All samples passed the acceptance criterion of not less than 2.20 lb.

Tip Electrode to Subassembly Crimp Strength: The crimp strength of thirty tip electrode to coil subassemblies was evaluated by pull testing. All samples passed the acceptance criterion of not less than 2.20 lb.

Neck to Tubing Bond Strength: For thirty samples, the bond strength between the molded rubber neck and the silicone rubber tubing was pull tested to confirm a minimum strength of 1.10 lb. All samples passed this minimum acceptance criterion.

Neck to Ring Bond Strength: The bond strength between the molded rubber neck and the electrode ring was measured on fifteen samples by pull tests. These tests confirmed that all samples passed the acceptance criterion of not less than 1.10 lb.

Neck to Tip Electrode Bond Strength: The bond strength between the molded rubber neck and the tip subassembly was pull tested on thirty samples. All samples passed the acceptance criterion of not less than 1.10 lb.

Tubing to Terminal Connector Bond Strength: The bond strength between the silicone rubber tubing and the terminal connector was measured on thirty samples by pull testing. Results confirmed that all samples passed the acceptance criterion of not less than 1.10 lb.

- FULL LEAD ASSEMBLIES (COMPLETED LEAD TESTING): Testing performed on full lead assemblies examined aesthetic quality, mechanical integrity, electrical integrity, and appropriate dimensions (length). Samples were tested to verify that the leads met product specifications. All samples met the test acceptance criteria. These results are summarized below.

Visual Inspection: Thirty leads were visually inspected to verify that aesthetic requirements were met. All samples passed the visual inspection criteria.

Pressure Testing: Thirty leads were pressure tested to evaluate the integrity of the molded and bonded sections. The test involved application of pressurized nitrogen gas through the terminal connector inner diameter inlet for a minimum of five seconds. The lead was immersed in a 70/30 isopropyl alcohol/distilled water solution during this test. All samples

passed the acceptance criterion of no bubbles observed in the solution from leaking nitrogen.

Resistance Testing: The direct current resistance was measured to assess continuity of the crimp and weld joints, and to measure the overall resistance of the lead. All leads met the acceptance criteria of 100 ± 10 ohms for the bipolar lead cathode circuit path (15 samples), 50 ± 5 ohms for the bipolar lead anode circuit path (15 samples) and 45 ± 5 ohms for the unipolar model cathode circuit path (15 samples).

Dimensional Testing: Thirty assembled leads were measured for appropriate lead length. All samples met the acceptance criteria of not less than 22.9 inches and not greater than 23.7 inches.

Dielectric Strength Testing: The insulation dielectric strength of thirty completed leads was evaluated by ramping up voltage supplied between the terminal connector and terminal ring using a Hipot tester. All leads met the acceptance criteria of withstanding 1500 ± 50 VAC for ten seconds without dielectric breakdown.

All subassemblies and full lead assemblies that underwent Process Validation Testing passed the test acceptance criteria.

3. Flex Fatigue Testing

Flex fatigue resistance testing consisted of mounting the conductor coils in a lead flex test fixture. Mid- and distal sections of the lead were evaluated to verify that they could withstand an equivalent of 10 years worth of flexing. Thirty-six conductor coils were flexed under ambient room conditions at specified radii and numbers of cycles. Another thirty-six conductor coils were flexed under wet conditions in saline at 37°C while being electrically pulsed. All lead conductors were required to withstand flex testing without fatigue failure which was defined as a physical break in the conduction path indicated by an increase in direct current (DC) resistance. The lead segments met the post-flex resistance acceptance criteria of remaining within 10% of the initial (pre-flex) resistance.

4. IS-1 Connector Testing

Connector performance testing was conducted in accordance with the IS-1 Standard ISO 5841-3(E). Dimensions measured on sixteen SELUTE lead connectors were within the dimensions specified in the IS-1 Standard. Insertion and withdrawal force testing, before (22 samples) and after (20 samples minimum) exposure to setscrew forces, involved inserting and withdrawing the lead connector from the lead connector go-gauge. The insertion and withdrawal force measurements could not exceed 14 N (3.15 lbs), as specified in the IS-1 Standard. All units passed the acceptance criterion of less than 3.1 lbs. Twenty-two connectors were subjected to electrical isolation testing to demonstrate adequate sealing in the connector cavity. The minimum electrical resistance between conductive elements intended to be electrically insulated by the sealing rings was to be 50 kilohms following a ten day soak, as specified by the IS-1 Standard. All samples passed the acceptance criterion.

5. Thermal/Humidity Resistance Testing

Since devices may experience temperature and humidity fluctuations during shipping, testing was conducted to demonstrate that the SELUTE Leads are resistant to thermal shock and humidity variations. Twelve packaged SELUTE leads were subjected to ten temperature cycles fluctuating between -55°C and +75°C. Testing conducted post-cycling included a visual inspection, final electrical testing, mechanical testing and drug plug analysis. There were no visual defects on twelve leads evaluated. Resistance measurements on twelve leads were within device specifications. Dielectric strength test results showed that current measured between conducting paths on six bipolar leads did not exceed 0.600 mA. Air pressure testing on twelve pressurized leads submerged in isopropyl alcohol and water did not show any leaks. Axial pull testing performed on 12 steroid leads demonstrated that all of the leads withstood a minimum axial tensile load of 1.1 lbf (0.50 Kgf) and exhibited no permanent deformation in excess of 5% of total lead length. Lastly, the amount of dexamethasone sodium phosphate in a drug plug from each of 12 leads was determined via UV Spectrophotometry. All drug plugs met the specification requirements of 0.45 - 0.95 mg.

6. Assessment of Drug Plug Dimensional Stability

Testing was conducted to assess the amount of swelling in four silicone drug plugs immersed in buffered saline at 37°C. Dimensional measurements were recorded after 6, 8.5, and 10.5 months of soak. A comparison of the initial drug plug dimensions and those following the 6 month soak showed a twofold increase in volume. Additional measurements on these same plugs at 8.5 and 10.5 months provided assurance that swelling was complete by 6 months. There were no changes in dimensions from the 6 month measurements. Therefore, matrix swelling in this study due to exposure to buffered saline was complete at or by 6 months. Also, the swelling that was observed did not exceed the dimensions of the SELUTE electrode cavity in which the drug plug is contained.

C. Biocompatibility

Biocompatibility testing of the finished SELUTE Lead was conducted in accordance with the FDA blue book memorandum #G87-1 entitled Tripartite Biocompatibility Guidance for Medical Devices, dated April 24, 1987. The tests conducted included Intracutaneous Toxicity, Sensitization, Cytotoxicity, Systemic Toxicity, Hemolysis, Pyrogenicity, Muscle Implant, Ames Mutagenicity, Subchronic Toxicity and Chronic Toxicity. The results of these tests showed that the leads are biocompatible and acceptable for human use.

D. In-Vivo (Animal) Tests

Thirty canines were implanted with a SELUTE Lead placed in the right ventricular apex (fifteen Model 4185/fifteen Model 4285) to verify the electrophysiologic performance of the SELUTE Lead with respect to pacing and sensing characteristics. Data was compared to the electrical performance of the CPI commercially available Model 4160/4260 porous tip lead, which served as the non-steroid control group. The control group was historical and consisted of thirteen devices (seven Model 4160/six Model 4260). Electrical data were taken at implant and at days 3, 7, 10, 14, 21, 28, 35, 42 and 49 post-implant. Information recorded included capacitor coupled voltage thresholds, constant current thresholds, current of injury, slew rate, R-wave amplitudes, R-wave sensing impedance and pacing impedance.

Results demonstrated lower and more stable voltage thresholds for the SELUTE leads than for the control leads. During the entire follow-up period the ventricular mean voltage thresholds for the steroid leads never exceeded 0.63 volts, whereas the control leads reached as high as 1.88 volts. Other pacing parameters such as R-wave amplitudes, slew rates and sensing/pacing impedances remained unchanged as compared to the controls.

Necropsy and histology examinations of SELUTE leads revealed typical observations and no abnormal growths or reactions. The steroid lead necropsy findings revealed an electrode well

fibrosed in the apex of the right ventricle in all cases. A small fibrotic sheath extended from the electrode within the range of 0.5 cm - 2 cm. Histological analyses showed that two leads had no evidence of reaction or inflammation of the lead in the myocardial wall or around the collar of connective tissue surrounding the lead. Two leads showed low-grade inflammatory reactions, one with some chronic inflammatory cells being incorporated in the mature connective tissue collar surrounding the lead. Two leads showed evidence for cartilaginous metaplasia in some areas where the lead had developed a connective tissue collar. Although a sterile aseptic scrub was performed on these animals prior to implant, there remains a possibility that these infectious processes began at the time of implant surgery, or were initiated during the course of the study by the transcutaneous pins entering the data block when taking data measurements.

Ten dogs (5 Model 4185/5 Model 4285) from the 49-day study were maintained in order to gather longer term (120 day) follow-up performance data. Pacing and sensing data were collected on these leads at 56, 63, 77, 91, 105 and 120 days post-implant. Results were compared to historical non-steroid control leads from dogs at 120 days post-implant (3 Model 4160/3 Model 4260). On average, stimulation thresholds for the steroid leads were lower than those for the non-steroid group. As demonstrated in the 49-day results, other pacing parameters such as R-wave amplitudes, slew rates and sensing impedance remained unchanged as compared to the controls. These animals were not sacrificed at 120 days and, therefore, no histology was performed as a part of this study.

E. Shelf-Life Tests (Bench and Animal)

Testing of leads subjected to accelerated aging was conducted to support the SELUTE lead 24-month shelf-life. Testing included 1) package testing to verify sterility, 2) electrical performance testing in animals to verify steroid efficacy in threshold reduction and appropriate lead function, 3) mechanical testing to verify maintenance of lead integrity, i.e., insulation integrity, axial pull strengths, etc. and 4) infrared spectroscopy to verify drug stability after aging.

1. Package Testing for Sterility

A total of 100 packages were involved in an accelerated aging study to evaluate the sterility barrier characteristics of the lead tray-in-tray packaging system. Twenty-five packages for the control group were initially sent out for ASTM shipping tests and these packages were then peel tested using an Instron tensile tester to determine the pull strength of the adhesive bond. Seventy-five lead packages were subjected to eight weeks of accelerated aging (equivalent to 48 months shelf-life). Fifty of these aged packages were then sent out for ASTM shipping tests, twenty-five of which were subsequently peel tested and 25 of which were dye penetrant tested. The remaining 25 aged packages were shipped to a contract testing and subjected to a microbial challenge after which sterility was verified. These studies confirm that the shipping tests do not produce any visible damage to the package, the aging process does not adversely affect the peel strength, and the integrity of the microbial seal is not adversely affected by the aging process.

2. Electrical Performance in Animals

Testing was conducted to establish the acute electrophysiologic performance, pacing and sensing characteristics, and general implant suitability of SELUTE Leads after aging. Ten sterilized and packaged SELUTE leads were exposed to ASTM D-4169 ship test conditions

(to simulate shipment) followed by exposure to elevated temperature and humidity conditions to accelerate equivalent to two years of ambient real-time aging. These leads were implanted in the left ventricular apex of dogs, one lead per animal. Voltage thresholds, current thresholds, pacing impedances, sensing impedances and R-wave amplitudes were measured at implant, 3, 7, 10, 14, 21 and 28 days post-implant. This data was then compared to historical control data available on 15 non-aged SELUTE leads and seven non-steroid market-released leads.

A comparison of the two year aged leads with the non-aged leads showed no significant difference ($p > 0.05$) between the two groups for voltage thresholds, current thresholds, pacing impedances, sensing impedances or R-wave amplitudes during the acute post-implant period (1 - 28 days). Therefore, the accelerated aging process had no effect on the performance of the SELUTE leads. Since the aged SELUTE leads performed the same as SELUTE leads with zero shelf age, this test data supports a shelf-life for the SELUTE Lead of 24 months.

3. Mechanical and Electrical Bench Tests for Lead Integrity

The purpose of this testing was to directly measure basic lead mechanical and electrical properties through bench testing. The bench tests performed were the same full lead tests conducted in original product evaluation testing for the SELUTE Lead. These tests were conducted on two-year aged SELUTE Leads (subjected to accelerated aging). The aged leads (twenty-four samples) were required to meet the same test acceptance criteria as the non-aged leads in the original design verification testing to examine whether any degradation had occurred. Results were as follows:

Lead Visual: Leads were visually inspected for surface imperfections and proper assembly using a microscope. All of the aged and non-aged leads met the visual requirements of the device specification.

Resistance Test: The direct current resistance was measured to assess continuity of the crimp and weld joints, and to measure the overall resistance of the lead. All leads, aged and non-aged, met the acceptance criteria of 100 ± 10 ohms for the bipolar lead cathode circuit path (Tips), 50 ± 5 ohms for the bipolar lead anode circuit path (anode) and 45 ± 5 ohms for the unipolar model cathode circuit path.

Stylet Insertion/Withdrawal Performance : Forces required to insert and withdraw stylets into and out of fully assembled leads were measured. A 0.016" diameter tapered stylet was inserted and withdrawn from each lead while the lead was straight. All leads, aged and non-aged, passed the acceptance criterion of not requiring more than 4.0 oz. of force for insertion or withdrawal.

Axial Pull Test: Following stylet insertion/withdrawal testing, the same leads were subjected to an axial pull test where a 1.1 lb weight was applied for up to 60 minutes, at which time the lead length was measured. After 60 minutes, the lead length was measured again. All specimens passed the acceptance criterion of no permanent deformation in excess of 5%.

Insulation Dielectric Strength: Insulation dielectric strength for the sensing/pacing cathode conduction path and the sensing/pacing anode conduction path was assessed on the leads that were subjected to the axial pull test. All assemblies passed the acceptance criterion of no current above 0.6 milliamps when 1500 VAC were applied between adjacent conductors.

These studies confirm that the aging process does not adversely effect the mechanical or electrical properties of the SELUTE Lead as measured through bench testing.

4. Drug Stability After Accelerated Aging

Aged steroid/silicone matrices (representing 6 years of shelf-life) were analyzed through Fourier Transform Infrared Spectroscopy (FTIR) and compared to non-aged steroid/silicone matrices to determine whether the drug composition had changed over time. These analyses showed comparable spectra for the aged and non-aged dexamethasone sodium phosphate (DSP) thus supporting no discernable change in the DSP composition after aging out to six years.

Results from the package sterility testing, the electrical performance testing in animals, the mechanical and electrical bench testing, and the steroid chemical analyses demonstrated that the aged SELUTE Leads showed no signs of degradation and continued to meet original design specifications. These results support a two-year shelf-life for the SELUTE Lead.

F. Clinical Studies

The SELUTE Steroid Eluting Lead was clinically evaluated to validate the safe and effective performance of the lead when used for cardiac pacing and sensing.

1. Objectives

The SELUTE clinical investigation had the following study objectives:

- (Primary) Validate that the acute (\leq 12-weeks post-implant) stimulation thresholds of the SELUTE lead is less than that of the non-steroid CPI control lead.
- Validate that chronic ($>$ 12-weeks post-implant) stimulation thresholds of the SELUTE lead are less than the non-steroid CPI control lead.
- Verify high impedance values ($>$ 500 ohms) of the SELUTE lead at acute and chronic stages post-implant.
- Demonstrate that the rate of morbidity and incidence of adverse effects for patients implanted with the SELUTE lead is no greater than the non-steroid CPI control lead.

- Verify the mechanical and electrical compatibility of the SELUTE lead with commercially available pulse generators.

2. Patient Population

A total of 233 patients were enrolled in the SELUTE IDE clinical investigation, resulting in 231 study implants. Patients were randomized at the time of implant in a 3:1 ratio between the SELUTE Model 4185/4285 lead and a comparable non-steroid control lead (CPI Models 4161/4261). A total of 178 patients received the SELUTE lead and 53 patients received the Control lead. Two patients were enrolled in the study, but did not receive study leads, due to anatomical abnormalities. (These patients were recorded as complications). (See Table 2)

A total of 20 U.S. clinical centers and six European clinical centers participated in the evaluation. The European study was conducted in compliance with the Declaration of Helsinki. The number of implants ranged from one lead per center to 27 leads, with a median number of lead implants of nine.

Table 2. Comparison of Patient Baseline Characteristics (n = 231)

Variables	SELUTE	Control	Statistics
Gender:			
Male	116 (65.2%)	33 (62.3%)	$\chi^2 = 0.15$ p = 0.70
Female	62 (34.8%)	20 (37.7%)	
Age (years):			
Range	25.8 - 94.8	21.6 - 93.6	t = 0.18 d.f. = 229 p = 0.86
Mean	71.4	71.1	
Standard deviation	10.1	13.2	
Pacing Indication:			
Atrial:			$\chi^2 = 1.19$, p = 0.28
Normal	63 (35.4%)	23 (43.4%)	
Disturbance	109 (61.2%)	28 (52.8%)	
None reported *	6 (3.4%)	2 (3.8%)	
AV node:			$\chi^2 = 0.47$, p = 0.49
Normal	50 (28.1%)	12 (22.6%)	
Disturbance	126 (70.8%)	39 (73.6%)	
None reported *	2 (1.1%)	2 (3.8%)	
Ventricular:			$\chi^2 = 0.60$, p = 0.44
Normal	101 (56.7%)	34 (64.2%)	
Disturbance	69 (38.8%)	18 (34.0%)	
None reported *	8 (4.5%)	1 (1.9%)	
Medications:			
None	45 (25.3%)	14 (26.4%)	$\chi^2 = 0.03$ p = 0.87
Drugs	133 (74.7%)	39 (73.6%)	
Presenting Symptoms:			
None	15 (8.4%)	4 (7.5%)	Fisher's exact test p = 1.00
Symptoms	159 (89.3%)	47 (88.7%)	
None reported *	4 (2.2%)	2 (3.8%)	
Medical History:			
None	37 (20.8%)	14 (26.4%)	$\chi^2 = 0.70$, p = 0.40
Cardiovascular disease	136 (78.6%)	38 (71.7%)	
None reported *	5 (2.8%)	1 (1.9%)	
Total Patients	178 (100.0%)	53 (100.0%)	231

* Not included in statistical analysis.

Gender Bias Analysis. Overall, women comprised 35.5% of the study subjects. This is comparable to the percentage of women who undergo pacemaker implantation in the general patient population (Sgarbossa et al, 1994; Shen et al, 1994; Tung et al, 1994). Differences between male and females in major study endpoints (pulse width, impedance) were examined. These results are presented below. There were no gender-related differences found.

Table 3. Comparison of Pulse Width Threshold at 2.5 V by Gender

Gender	SELUTE Patients		Control Patients		ANOVA
	n	Mean (Std Dev)	n	Mean (Std Dev)	
Male	108	0.10 (0.15)	28	0.21 (0.08)	F = 0.4 p = 0.53
Female	61	0.09 (0.06)	17	0.18 (0.09)	

Table 4. Comparison of Impedance by Gender

Gender	SELUTE Patients		Control Patients		ANOVA
	n	Mean (Std Dev)	n	Mean (Std Dev)	
Male	106	660.2 (131.7)	28	704.9 (88.8)	F = 0.86 p = 0.36
Female	61	632.6 (98.0)	17	731.3 (123.1)	

3. Study Design and Comparison Study Group

The SELUTE clinical investigation contained a concurrent, randomized Control group comprised of patients receiving a CPI Model 4161 or 4261 lead. These leads are identical to the SELUTE unipolar and bipolar counterparts, except for the presence of the steroid drug and silicone release matrix in the lead tip, and the spacing of the ring electrodes in the bipolar version (11 mm in the SELUTE and 28 mm in the Control).

The subjects enrolled in the study were randomized in a ratio of three patients to the SELUTE group to one patient for the Control. This proportional randomization was chosen as a study design to maximize the information gained on the new SELUTE device, at the requirement of a slightly larger overall sample size. The study was designed to detect a minimum difference in the pulse width threshold at two weeks between the SELUTE and Control leads of 35% of the measured Control value. The required sample for the study was estimated with a Type I error of 0.05 and a power of 90% to detect the minimum difference.

The effectiveness of the randomization in balancing patient demographic and prognostic factors was examined. All variables evaluated, showed no significant difference ($p > 0.05$) between the

two study arms. Those variables showing no difference included age, gender, pacing indications (atrial, A-V junction, ventricular), use of medications, and presenting symptoms. Overall, the analysis showed an effective balance achieved with the randomization.

4. Study Results

Statistical Analysis. Descriptive statistics were used to analyze the data gathered in the clinical study and to summarize the results. Data were gathered from multiple centers following the requirements of a common treatment and data collection protocol. For discrete variables including gender, primary arrhythmia, and concomitant medications, frequency distributions and cross tabulations were used to analyze and present the data. For continuous variables (e.g., patient age, number of implant months) means, standard deviations, and ranges, as well as frequency distributions were used to examine and present the data.

For comparisons between two groups, Pearson chi-square or Fisher exact tests were used for categorical data. When continuous variables were examined, Student's t-tests (either independent or paired sample tests) were used for testing mean differences between two groups, and analysis of variance techniques (ANOVA) when there were more than two groups. Statistical tests were all two-sided tests of the study hypotheses, and the significance level (Type I error) was set at value of 0.05.

Prior to the statistical analysis of study findings, data from the U.S. and European centers participating in the investigation were examined to justify the pooling of study results. Each study objective was stated in terms of testable statistical hypotheses, which were evaluated using analysis techniques appropriate to the type of endpoint and distributional characteristics present.

a. Pacing Thresholds

At all follow-up intervals (two weeks, four weeks, six weeks, 12 weeks, and six months) and at all voltages tested (0.8, 1.6, 2.5, and 5.0 volts) the pulse width thresholds were significantly lower (all p-values < 0.001) with the SELUTE lead than with the Control lead. These reductions were in the range from 41% to 62% for the typical pacing voltage of 2.5 volts.

To confirm continued long-term reduction in stimulation threshold for the SELUTE lead, a single threshold test at 1.6 V was conducted for follow-ups occurring after 6 months. Mean chronic threshold data are presented in Table 5. At one year post-implant, SELUTE thresholds remained relatively stable and significantly lower (38%) compared to that of the control lead (p < 0.003). In contrast, the mean threshold for the control lead is still decreasing. This indicates that the lower chronic thresholds for the SELUTE lead are achieved earlier during the lead maturation process.

Table 5. Mean Chronic Threshold at 1.6 Volts (n = 231)

Follow-Up Period	SELUTE			Control			Comparison		
	Mean (ms)	Std Dev	n	Mean (ms)	Std Dev	n	t-Test	p-Value	Difference
12 Weeks	0.16	0.22	158	0.37	0.31	41	4.97	< 0.001**	-56.8%
6 Month	0.15	0.11	135	0.33	0.26	39	6.34	< 0.001**	-54.5%
12 Month	0.18	0.14	104	0.29	0.25	30	3.06	< 0.003**	-37.9%

** Extremely statistically significantly different (p < 0.001).

b. Lead Impedance

Table 6 shows the mean lead impedance for the SELUTE and control lead groups. Overall, average SELUTE lead impedance tends to be lower than that of the control lead, but remains above the 500 ohm level both acutely and after lead maturation. The mean impedance at 12 months post-implant for the SELUTE lead was 678 ohms compared to 763 ohms for the

control lead. This is consistent with previous published studies that demonstrated lower impedance for steroid leads versus comparable non-steroid leads.

Table 6. Lead Impedance Measurements at 5.0 V and 0.5 ms

Follow Up	SELUTE				Control			
	Mean	Std Dev	n	p-Value*	Mean	Std Dev	n	p-Value*
At implant	696	106.8	171	< 0.05	711	115.8	53	< 0.05
2 Weeks	697	93.3	168	< 0.05	721	84.7	47	< 0.05
4 Weeks	714	95.5	163	< 0.05	758	100.2	46	< 0.05
6 Weeks	720	94.9	160	< 0.05	774	91.6	48	< 0.05
12 Weeks	701	94.9	157	< 0.05	771	90.4	42	< 0.05
6 Months	695	91.9	135	< 0.05	781	93.8	40	< 0.05
12 Months	678	96.0	111	< 0.05	763	124.8	33	< 0.05

* Statistically significant (p < 0.05). Student-T test, comparison to 500 ohms.

c. Compatibility

There were no observed problems with either study lead in terms of achieving proper mechanical connections to the different pulse generators used in the investigation. An evaluation of the R-wave amplitudes measured from the study leads showed no difference between the SELUTE and Control at either two weeks post-implant (p = 0.60) or at six months (p = 0.54). This is evidence that the SELUTE lead is sensing intracardiac signals in an appropriate manner, comparable to those obtained with the market-released Control leads.

d. Clinical Adverse Events (Observations and Complications)

A clinical complication is defined as a clinical event that results in invasive intervention, injury, or death. A clinical observation is defined as a clinical event that is not classified as a complication. Each observation and complication is classified as one of the following four types:

- Type I: Related to the implanted device and/or a system component
- Type II: Related to the labeling of the device and/or labeling of a system component
- Type III: Not related to the implanted device, system component, or labeling but would not have occurred in the absence of the implanted device and/or system component
- Type IV: Change in patient's condition

Seven complications were reported in the study. None of the complications were considered to represent unanticipated adverse effects and were typical risks shared by all patients receiving an implantable pacing system (See Table 7).

Table 7. Reported Clinical Complications (n = 231 patients)

Complication	SELUTE	Control	Study Total	Device-Related
Lead dislodgment, post-implant	2	0	2	2
Infection (procedure-related)	1	1	2	0
Pneumothorax (procedure-related)	1	0	1	0
Placement difficulty (anatomical)	1	0	1	0
Insertion tool difficulty (anatomical)	0	1	1	0
Total Complications	5	2	7	2

Device-related = SELUTE or control lead.

Clinical observations are summarized below, in Tables 8 and 9. Fifty-four observations were reported, including a total of 14 Type I observations, 12 of which were considered to be device-related

(9 SELUTE, 3 control). All observations were resolved and were typical of the risks shared by all patients receiving an implantable pacing system. There were no unanticipated adverse effects.

Table 8. Summary of Type I Observations (n = 231 patients)

Type I Observations	SELUTE	Control	Study Total	Device-Related
Infection (procedure-related)	2	0	2	0
Thrombosis (procedure-related)	1	0	1	1
Difficulty positioning lead	2	1	3	3
Elevated threshold at implant, ventricle	1	1	2	2
Excessive change in impedance	1	0	1	1
Loss of capture, ventricle	1	0	1	1
T-wave oversensing	2	0	2	2
Undersensing, ventricle	1	1	2	2
Total Type I Observations:	11	3	14	12

Device-related = SELUTE or control lead.

The incidence rate of reported observations and complications was calculated as a function of the implant time for the two devices. No significant difference between the two study groups was found with respect to complications ($p = 0.70$), total observations ($p = 0.30$), or any of the subgroups of observations.

Table 9. Comparison of Complication Rate (n = 231 patients)

Group	SELUTE		Control		Comparison
	Number	Incidence Rate	Number	Incidence Rate	
Complications	5	0.0016	2	0.00222	$z = 0.38, p = 0.70$
Type I observations	11	0.0036	3	0.0033	$z = 0.11, p = 0.92$
Type III observations	9	0.0029	1	0.0011	$z = 0.95, p = 0.34$
Type IV observations	25	0.0081	5	0.0056	$z = 0.78, p = 0.44$
Total observations	45	0.0146	9	0.0100	$z = 1.04, p = 0.30$

* Statistically significant ($p \leq 0.05$).

Incidence rate: SELUTE 3076 patient months, control 897 patient months.

XI. DEVICE ACCOUNTABILITY, RELIABILITY AND LONGEVITY

Nineteen leads were removed from service during the clinical study. None of the leads were returned to CPI for analysis. The leads were either interred with the patients (deaths) or capped and remained implanted in the patient.

Table 10. Out-of-Service Devices (n = 231)

Reason for Removal from Service	SELUTE	Control	Study Total
Infection	1	1	2
Dislodgment	1	0	1
Heart Transplant	1	0	1
Patient Death	12	3	15
TOTAL	15	4	19

There were no SELUTE lead failures reported in the clinical study. Worldwide experience is that the failure rate for the SELUTE lead, based on data as of 10/26/95, is less than 0.0011% per month (no confirmed failures based upon returned devices).

XII. CONCLUSIONS DRAWN FROM THE STUDIES

The *in vitro* electrical and mechanical bench test results provide reasonable assurance that the SELUTE Lead, Models 4185/4285, meet design specifications and are reliable.

Animal studies indicate that the SELUTE Lead, Models 4185/4285, is effective in reducing acute and chronic pacing threshold in canines from those observed for a commercially available non-steroid control lead. Furthermore, necropsy and histology did not show any adverse or unexpected biological responses with the SELUTE lead.

The results of the clinical studies provide reasonable assurance that the SELUTE lead, Models 4185/4285, is safe and effective when it is used as indicated in the labeling. Acute and chronic low thresholds have been verified for the SELUTE lead.

XIII. PANEL RECOMMENDATION

Pursuant to section 515(f) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, as an FDA advisory panel, for review and recommendation because the information in the PMA substantially duplicated information previously reviewed by this panel.

XIX. CDRH DECISION

FDA issued an approval order on May 8, 1996. The sponsor's manufacturing facility was inspected on October 3 and 25, 1995 and was found to be in compliance with the device Good Manufacturing Practice regulations.

XX. APPROVAL SPECIFICATIONS

Directions for use: See the labeling (Attachment 1)

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling (Attachment 1).

Post-approval Requirements and Restrictions: See approval order (Attachment 2)