

Summary of Safety and Effectiveness Data

1. GENERAL INFORMATION

Device Generic Name: Replacement heart valve

Device Trade Name: Carpentier-Edwards™ S.A.V.™ Bioprosthesis, Model 2650 (Aortic)

Applicant Name and Address: Edwards Lifesciences LLC
One Edwards Way
Irvine, CA 92614

PMA Application Number: P010041

Date of Panel Recommendation: None

Date of Notice of Approval to the Applicant: June 24, 2002

2. INDICATIONS FOR USE

The Carpentier-Edwards S.A.V. Bioprosthesis Model 2650 is indicated for patients who require replacement of their native or prosthetic aortic valve.

3. DEVICE DESCRIPTION

The Carpentier-Edwards S.A.V. Bioprosthesis Model 2650 is a trileaflet stent-supported bioprosthetic valve comprised of porcine aortic valve tissue mounted on a flexible frame. The bioprosthesis is processed with the XenoLogiX Treatment, which uses ethanol and polysorbate-80 (a surfactant), and is packaged and terminally sterilized in glutaraldehyde. Glutaraldehyde is shown to both reduce the antigenicity of tissue xenograft valves and increase tissue stability; however, glutaraldehyde alone has not been shown to affect or reduce the calcification rate of the valve. The preservation or “fixation” of the valve is performed under 0 to 4 mmHg pressure to minimize alterations in the collagen waveform of the aortic valve tissue.

The flexible frame or wireform of the valve is composed of Elgiloy and is covered with a polytetrafluoroethylene (PTFE) cloth. It is designed to be compliant at the orifice and commissures to reduce the closing loading shocks at the commissures and free margin of the leaflets.

A polyester film band surrounds the base of the wireform frame. A suture ring covered with PTFE cloth is attached to the wireform frame. The suture ring contains inserts of silicone rubber and non-woven polyester. Two parallel marking sutures are located on the suture ring to denote the smallest intercommissural distance and are intended to aid in the proper orientation of the prosthesis.

The Carpentier-Edwards S.A.V. Bioprosthesis Model 2650 is designed for supraannular placement in the aortic position. The valve is available in mounting diameter sizes 21, 23, 25, and 27 mm.

4. CONTRAINDICATIONS

None known.

5. WARNINGS AND PRECAUTIONS

A listing of warnings and precautions can be found in the device labeling.

6. ALTERNATIVE PRACTICES AND PROCEDURES

The alternative to the Carpentier-Edwards S.A.V. Bioprosthesis Model 2650 is surgical replacement of the malfunctioning aortic valve with an allograft or another prosthetic replacement heart valve for which there is an approved premarket approval application (PMA). When a replacement heart valve is chosen as the appropriate therapy, the option of choosing between a mechanical or biological valve prosthesis exists. The choice of replacement heart valve depends on an assessment of patient factors that include age, preoperative condition, anatomy, and the patient's ability to tolerate long-term anticoagulant therapy.

Other forms of treatment may include the use of cardiac drug therapy or other types of surgical treatment, such as native valve reconstruction or modification.

7. MARKETING HISTORY

The Carpentier-Edwards S.A.V. Bioprosthesis Model 2650 is currently available in Australia, Austria, Belgium, Canada, Chile, China, Denmark, Egypt, Finland, France, Germany, Greece, Hong Kong, India, Ireland, Israel, Italy, South Korea, Luxembourg, Malaysia, Netherlands, New Zealand, Norway, Pakistan, Portugal, Singapore, South Africa, Spain, Sweden, Switzerland, Thailand, Turkey, the United Kingdom, and Uruguay.

The Carpentier-Edwards S.A.V. Bioprosthesis Model 2650 has not been withdrawn from marketing in any country for any reason relating to the safety and/or the effectiveness of the device.

8. ADVERSE EVENTS

Two multi-center, non-randomized, clinical studies were conducted. The first study was a long-term, mostly retrospective and partially prospective evaluation of 217 patients implanted with the Carpentier-Edwards S.A.V. Aortic Bioprosthesis Model 2650 at 3 centers and was conducted between 1991 and 1999. The second study was a short-term, prospective evaluation of 151 patients implanted with the Carpentier-Edwards S.A.V. Aortic Bioprosthesis Model 2650 between 1990 and 1994. The enrollment periods for the two studies overlapped at one center resulting in a pooled co-hort of 337 patients at 5 centers with one center participating in both studies. In the long-term study, patients were evaluated preoperatively, intraoperatively, at discharge, and at periodic intervals thereafter. In the short-term study, patients were evaluated preoperatively, intraoperatively, at discharge, at 3 to 6 months, and at 1 year. Adverse events were captured throughout the postoperative period. The cumulative follow-up was 1392.9 patient-years with a mean follow-up of 4.1 years (SD=3.1 years, range=0 to 8.8 years).

A total of 89 deaths (11 early, 78 late) occurred during the study and 23 of these were characterized as valve related. The cause of the valve related deaths were cardiac arrest/unknown (10 patients), anticoagulant-related hemorrhage (5 patients), endocarditis (4 patients), thromboembolism (3 patients), and structural valve deterioration (1 patient).

8.1 Observed Adverse Events

Adverse events were reported in the pooled clinical study as shown in the following table.

Table 8.1-1.: Observed Adverse Event Rates for AVR

All patients analyzed: N= 337 Cumulative follow-up: 1392.9 patient-years

Complication	Early Events		Late Events ¹		Freedom from Event (%) ± 95% CI ²		
	n ³	%	n	%/pt.-yr.	1 year (n = 269-281)	5 years (n = 137-153)	8 years (n =24-31)
Mortality (all)	11	3.3	78	5.71	93.6 ± 2.8	74.1 ± 6.0	59.5 ± 13.3
Valve-related events							
Valve-related mortality	2	0.6	21	1.54	98.8 ± 1.3	92.1 ± 4.1	87.4 ± 10.9
Explant	0	0.0	5	0.37	99.4 ± 0.9	98.4 ± 2.0	97.2 ± 5.8
Reoperation ⁴	0	0.0	0	0.00	100 ± 0.0	100 ± 0.0	100 ± 0.0
Bleeding	3	0.9	28	2.05	98.8 ± 1.3	91.5 ± 4.4	82.3 ± 12.6
Endocarditis	0	0.0	12	0.88	99.0 ± 1.1	97.0 ± 2.7	95.6 ± 7.1
Hemolysis	0	0.0	0	0.00	100 ± 0.0	100 ± 0.0	100 ± 0.0
Nonstructural dysfunction	0	0.0	2	0.15	99.7 ± 0.7	99.3 ± 1.4	99.3 ± 3.0
Perivalvular leak	0	0.0	3	0.22	99.7 ± 0.7	98.8 ± 1.8	98.8 ± 3.9
Structural valve deterioration	0	0.0	4	0.29	100 ± 0.0	99.5 ± 1.1	96.2 ± 6.6
Thromboembolism	6	1.8	36	2.64	96.5 ± 2.2	89.0 ± 5.0	83.3 ± 13.6
Valve thrombosis	0	0.0	0	0.00	100 ± 0.0	100 ± 0.0	100 ± 0.0

Notes:

1. Late event rates were calculated as linearized rates (%/pt-yr) based on 1366.2 late patient-years (>30 days postoperatively).
2. Freedom from event rates were calculated using the Kaplan-Meier method. Peto's formula was used for calculation of the 95% confidence intervals.
3. n = number of patients
4. Includes reoperation without valve explant.

8.2 Potential Adverse Events

Adverse events potentially associated with the use of bioprosthetic heart valves include:

- Angina
- Cardiac Arrhythmias
- Endocarditis
- Heart failure
- Hemolysis
- Hemolytic anemia
- Hemorrhage
- Myocardial infarction
- Prosthesis leaflet entrapment (Impingement)
- Prosthesis nonstructural dysfunction
- Prosthesis pannus
- Prosthesis perivalvular leak
- Prosthesis regurgitation
- Prosthesis structural deterioration
- Prosthesis thrombosis
- Stroke
- Thromboembolism

It is possible that these complications could lead to:

- Reoperation
- Explantation
- Permanent Disability
- Death

9. SUMMARY OF NONCLINICAL STUDIES

9.1 *In vitro* Testing

In vitro studies were performed for the Carpentier-Edwards S.A.V. Bioprosthesis Model 2650 as recommended in the FDA's *Draft Replacement Heart Valve Guidance* (1994). Although tested in the nonclinical studies, the clinical studies (Section 10) did not generate sufficient data to support the safety and effectiveness of sizes 19, 29, and 31 mm aortic valves. The data from the preclinical testing of these sizes are included in the summaries below since the results were used in the overall evaluation of the approved devices.

9.1.1 Biocompatibility Studies

Biocompatibility testing of all implantable non-biological component materials used in the S.A.V. Model 2650 bioprosthesis were performed in accordance with the requirements of ISO 10993-1, with the exception of carcinogenicity testing. Carcinogenicity testing was determined to be unnecessary because the test articles demonstrated no mutagenic potential at levels at or above those intended for the clinical application. All studies were performed by Edwards Lifesciences LLC, Irvine, CA, in accordance with the FDA GLP Regulations (21 CFR Part 58) unless otherwise noted. Those studies identified as non-GLP evaluations were conducted in accordance with GLP regulations in that strict compliance to standard operating procedures was maintained; however, the protocol, final report, QAU audits, and record storage were not in strict compliance 21 CFR Part 58. A matrix of the tests performed are provided in **Table 9.1.1-1**. Test samples for the biocompatibility studies identified in Table 9.1.1-1 were exposed to ethylene oxide, steam, glutaraldehyde and formaldehyde to simulate a worst-case exposure. All test were performed using surface area exposure in excess of that found in the finished device.

The glutaraldehyde fixed porcine aortic valve tissue has an extensive clinical history in bioprosthetic heart valves and has demonstrated freedom from complications related to biocompatibility. *In vivo* animal implantation results and long-term clinical safety results accumulated on the S.A.V. valve support the biocompatibility of the finished device.

The non-implantable valve components and accessories including holders, sizers, and handles were subjected to a battery of toxicity tests appropriate for these devices. All results were found to be acceptable.

Table 9.1.1-1: Biocompatibility Tests and Results

Test Performed	Test Objective	Samples: Control	Samples: S.A.V.	Results
<i>In vitro</i> Cytotoxicity (Inhibition of Cell Growth Test)	Assess the effect of the aqueous extract of a material on the normal growth of cells in culture. The sample is considered non-inhibitory to cell growth if the percent of inhibition is equal to or less than 29%.	Negative control only: Water	Silicone Rubber Elgiloy® Alloy Polyethylene terephthalate (PET) cloth & film Polytetrafluoroethylene (PTFE) cloth & thread	Non-inhibitory to cell growth. 15.2% inhibition. Non-inhibitory to cell growth. 0% inhibition. Non-inhibitory to cell growth. 0% inhibition. Non-inhibitory to cell growth. 0% inhibition.

Table 9.1.1.-1: Biocompatibility Tests and Results

Test Performed	Test Objective	Samples: Control	Samples: S.A.V.	Results
			Silk suture thread	Non-inhibitory to cell growth at a concentration representative of that used in the device. Inhibitory to cell growth at elevated sample concentrations.
<i>In vitro</i> Cytotoxicity (Medium Eluate Method Test)	Evaluate the cytotoxic effects of a material growth medium extract on a human fibroblast monolayer. A sample is judged non-cytotoxic if lysis is not greater than the negative control.	Negative Control: Cell growth medium Positive Control: Approximately 5% Ethanol in water	Silicone Rubber Elgiloy® Alloy Polyethylene terephthlate (PET) cloth & film Polytetrafluoroethylene (PTFE) cloth & thread Silk suture thread	Non-cytotoxic to cells. 0% cell lysis. Non-cytotoxic at concentrations representative of that used in the device. Cytotoxic at concentrations above those used on the device.
<i>In vitro</i> Cytotoxicity (Agar Overlay Test) <i>Continued from previous page</i>	Evaluate the cytotoxicity of diffusible components of a material through an agar overlay assay. A sample is judged non-cytotoxic if lysis is not greater than the negative control.	Negative control: Polypropylene solid sample Positive control: Polyvinyl chloride (PVC) with organotin	Silicone Rubber Elgiloy® Alloy Polyethylene terephthlate (PET) cloth & film Polytetrafluoroethylene (PTFE) cloth & thread Silk suture thread	Non-cytotoxic to cells. 0% cell lysis. Non-cytotoxic to cells. 0% cell lysis. Non-cytotoxic to cells. 0% cell lysis. Non-cytotoxic to cells. 0% cell lysis. Moderate to severe cytotoxicity (20% to 60% cell lysis). Cytotoxicity at elevated sample concentrations above those used in the final device due to glutaraldehyde and formaldehyde residuals present in the solid sample and under the static environments imposed in this <i>in vitro</i> test. The same material without chemical exposure was determined to be non-cytotoxic.
Haemo-compatibility (ASTM Blood Compatibility)	Determine the extract and solid sample to be non-hemolytic (< 5% hemolysis) and for the extract to have no effect (within 5% of the negative control) on the clotting time.	Negative control extract: Normal saline Negative control solid sample: Polyethylene Positive control extract and solid sample: None used per standard procedure Negative control: Normal saline Positive control: None	Silicone Rubber Elgiloy® Alloy Polyethylene terephthlate (PET) cloth & film Polytetrafluoroethylene (PTFE) cloth & thread	Non-hemolytic to blood and has no adverse effect on clotting time Non-hemolytic to blood and has no adverse effect on clotting time Non-hemolytic to blood and has no adverse effect on clotting time Non-hemolytic to blood and has no adverse effect on clotting time

Table 9.1.1.-1: Biocompatibility Tests and Results

Test Performed	Test Objective	Samples: Control	Samples: S.A.V.	Results
		used per standard procedure	Silk suture thread	Non-hemolytic to blood and has no adverse effect on clotting time. One hemolytic result due to glutaraldehyde and formaldehyde residuals present in these exaggerated sample sizes and under the static environments imposed in this <i>in vitro</i> test.
<i>In vitro</i> Genotoxicity (Ames Test-Plate Incorporation and Spot Test) <i>Continued from previous page</i>	Detect the presence of mutagenic moieties in biomaterials using non-activated and activated systems	Negative control: Normal saline or the corresponding medium used for the test article extraction. Positive control (non-activated system): Bacterial Strain TA97; ICR-191 Acridine Mutagen in DMSO (1.0 mg/plate); TA98: 2-Nitrofluorene in DMSO (10.0 mg/plate); TA100: Sodium Azide in distilled water (7.0 mg/plate); TA102: Mitomycin C in distilled water (0.5 mg/plate). Positive control (activated system): TA97: 2-Aminofluorene in DMSO (10.0 mg/plate); TA98: 2-Aminoanthracene in DMSO (1.5 mg/plate); TA100: 2-Aminoanthracene in DMSO (1.5 mg/plate); TA102: Danthron in DMSO (30.0 mg/plate)	Silicone Rubber	Non-mutagenic using activated and non-activated systems.
			Elgiloy® Alloy	Non-mutagenic using activated and non-activated systems.
			Polyethylene terephthlate (PET) cloth & film	Non-mutagenic using activated and non-activated systems.
			Polytetrafluoroethylene (PTFE) cloth & thread	Non-mutagenic using activated and non-activated systems.
			Silk suture thread	Non-mutagenic using activated and non-activated systems.
<i>In vitro</i> Genotoxicity (Sister Chromatid Exchange Test)	Detect the presence of mutagenic moieties in biomaterials using non-activated and activated systems.	Negative control: Distilled water or the corresponding medium used for the test article extraction. Positive control (non-activated system): Distilled water with mitomycin C @ 0.005 µg/mL.	Silicone Rubber Elgiloy® Alloy Polyethylene terephthlate (PET) cloth & film Polytetrafluoroethylene (PTFE) cloth & thread	Non-mutagenic using activated and non-activated systems. Non-mutagenic using activated and non-activated systems. Non-mutagenic using activated and non-activated systems. Non-mutagenic using activated and non-activated systems.

Table 9.1.1.-1: Biocompatibility Tests and Results

Test Performed	Test Objective	Samples: Control	Samples: S.A.V.	Results
		Positive control (activated system): Distilled water with cylophosphamide @ 1.0 µg/mL.	Silk suture thread	Non-mutagenic at all concentrations using the activated system and at concentrations representative of the final device using the non-activated system.
Systemic Toxicity (USP Mouse Systemic Injection Test)	Evaluate the systemic effect of a material extract in mice. The sample is considered systemically non-toxic if all the mice treated with the sample extract survive at the end of 72 hours and none shows an outward symptom of greater rejection or weight change than mice treated with the negative control.	Negative control: Normal saline and vegetable oil or the corresponding medium used for the test article extraction	Silicone Rubber Elgiloy® Alloy Polyethylene terephthlate (PET) cloth & film Polytetrafluoroethylene (PTFE) cloth & thread Silk suture thread	All mice normal. Non-toxic. All mice normal. Non-toxic. All mice normal. Non-toxic. All mice normal. Non-toxic. All mice normal. Non-toxic.
Irritation or Intracutaneous Reactivity (Rabbit Intracutaneous Reactivity Test)	Evaluate the effects of a material extract in contact with dermis of rabbits. The sample is considered non-irritating if the average erythema/edema rating for any given time is not remarkably greater than that for the negative control.	Negative control: Normal saline and vegetable oil or the corresponding medium used for the test article extraction	Silicone Rubber Elgiloy® Alloy Polyethylene terephthlate (PET) cloth & film Polytetrafluoroethylene (PTFE) cloth & thread Silk suture thread	All rabbits normal. Non-irritating. All rabbits normal. Non-irritating. All rabbits normal. Non-irritating. All rabbits normal. Non-irritating. All rabbits normal. Non-irritating.
Implantation (Rabbit Intramuscular Implantation Test) Addresses both the subchronic and chronic test requirements.	Evaluate the effect of direct exposure of the test material when implanted into the paravertebral muscle of rabbits for 7, 30, 60, or 90 days. A material is biocompatible if there is no gross visible evidence of tissue damage and if histopathological examination shows no signs of chemical-induced cytotoxicity.	Negative control: Polyethylene 306	Silicone Rubber Elgiloy® Alloy Polyethylene terephthlate (PET) cloth & film Polytetrafluoroethylene (PTFE) cloth & thread Silk suture thread	Material is biocompatible (sub-chronic and chronic evaluations) with no signs of chemical-induced cytotoxicity. Material is biocompatible (sub-chronic and chronic evaluations) with no signs of chemical-induced cytotoxicity. Material is biocompatible (sub-chronic and chronic evaluations) with no signs of chemical-induced cytotoxicity. Material is biocompatible (sub-chronic and chronic evaluations) with no signs of chemical-induced cytotoxicity. Material is biocompatible (sub-chronic and chronic evaluations) with no signs of chemical-induced cytotoxicity.
Guinea pig maximization test	Evaluate the potential of material to produce sensitization when the material saline extract is	Negative control: Normal saline and vegetable oil or the corresponding medium used for the test	Silicone Rubber Elgiloy® Alloy	All guinea pigs normal. Non-sensitizing. All guinea pigs normal. Non-sensitizing.

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Table 9.1.1.-1: Biocompatibility Tests and Results

Test Performed	Test Objective	Samples: Control	Samples: S.A.V.	Results
	repeatedly exposed to guinea pigs. A material is considered to possess no apparent sensitizing properties if the erythema and edema score is not remarkably greater than the negative control.	article extraction	Polyethylene terephthlate (PET) cloth & film Polytetrafluoroethylene (PTFE) cloth & thread Silk suture thread	All guinea pigs normal. Non-sensitizing. All guinea pigs normal. Non-sensitizing. All guinea pigs normal. Non-sensitizing.

9.1.2 Hydrodynamic Performance

Comprehensive *in vitro* hydrodynamic performance studies of the Model 2650 S.A.V. bioprotheses were performed. An extensive battery of tests (Steady forward flow, Steady backflow leakage, Pulsatile flow pressure drop, Pulsatile flow regurgitation, Flow visualization, and Verification of the Bernoulli relationship) were conducted to evaluate valve performance under steady and pulsatile flow testing conditions. Medtronic Model 242 Hancock or Carpentier-Edwards Model 2625 bioprotheses were used as reference valves in studies requiring concurrent testing of a porcine tissue valve marketed in the U.S. The studies were conducted in accordance with the *FDA Draft Replacement Heart Valve Guidance* (1994) or *ISO 5840, Cardiovascular Implants-Cardiac Valve Prothesis* (1989). A matrix of the test performed and corresponding results are provided in **Table 9.1.2.-1**.

Table 9.1.2.-1: Hydrodynamic Testing and Results

Test	Sample Size: S.A.V. Model 2650	Sample Size: Reference	Results
Steady Forward Flow Pressure Drop Evaluation**	Three each of the following sizes: 19mm, 21mm, 23mm, 25mm, 27mm, 29mm, 31mm.	One 19mm and one 31mm Model 242 Hancock Valve	The S.A.V. aortic valve demonstrates a low resistance to forward flow, as demonstrated by lower pressure gradients when compared to the reference valves.
Steady Backflow Leakage Evaluation*	Three each of the following sizes: 19mm, 21mm, 23mm, 25mm, 27mm, 29mm, 31mm.	One 25mm Carpentier-Edwards Bioprothesis Model 2625	The S.A.V. aortic valve provides adequate resistance to backflow as demonstrated by the overall reduced leakage rates compared to the reference valve of the same size. The leakage rate for all valves was <5mL/sec, which is considered trivial.
Pulsatile Flow Pressure Drop Evaluation**	Three each of the following sizes: 19mm, 21mm, 23mm, 25mm, 27mm, 29mm, 31mm.	One 23mm Model 242 Hancock Valve	The S.A.V. aortic valve offers a low resistance to pulsatile forward flow for all sizes, as indicated by low pressure gradients and large effective orifice areas (EOA). The S.A.V. valve demonstrates lower pressure gradients and larger EOAs compared to the reference valves of the same size at cardiac outputs up to 7 L/min.
Pulsatile Flow Regurgitation Evaluation**	Three each of the following sizes: 19mm, 21mm, 23mm, 25mm, 27mm, 29mm, 31mm.	One 23mm Model 242 Hancock Valve	The closing, leakage, and total regurgitant volumes were low for all valves. The total regurgitant volumes for each valve remained relatively constant at all cardiac outputs regardless of cycle rate. The performance of the S.A.V. aortic valve is comparable to the Hancock reference valve of the same size in terms of resistance to retrograde flow.
Flow Visualization*	One 19mm	Not Applicable	The S.A.V. aortic valve demonstrated acceptable flow patterns. No flow stasis was observed during opening or closing.
Verification of Bernoulli Relationship*	One 19mm	Not Applicable	The transvalvular pressure drop results for the S.A.V. aortic valve obtained by Doppler ultrasonography and transducer demonstrated very good overall correlation.

* Study conducted in accordance with *FDA Draft Replacement Heart Valve Guidance* (1994)

** Study conducted in accordance with *ISO 5840, Cardiovascular Implants-Cardiac Valve Prothesis* (1989)

9.1.3 Structural Performance

In vitro structural performance studies of the Carpentier-Edwards S.A.V. Bioprosthesis Model 2650 were performed in accordance with *FDA Draft Replacement Heart Valve Guidance* (1994). A Carpentier-Edwards Bioprosthesis (C.E.P.B.) Aortic Model 2625 porcine valve was used as a reference in studies requiring concurrent testing of a tissue valve marketed in the U.S. A matrix of tests performed, and corresponding results is provided in **Table 9.1.3.-1**.

Table 9.1.3.-1: Structural Performance Evaluation

Test	Sample Size: S.A.V. Model 2650	Sample Size: Reference C.E.P.B. Model 2625	Results
Accelerated Wear	Three each of the following sizes: 19mm, 25mm, 31mm.	One each of the following sizes; 19mm, 25mm, 31mm.	All of the S.A.V. aortic valves offered satisfactory <i>in vitro</i> durability performance out to 5 equivalent years (200 Mcycles) of accelerated wear testing. Valves displayed good opening and closing throughout durability testing.
Dynamic Failure Mode	One each of the following sizes: 19mm, 25mm, 31mm. (Previously used in Accelerated Wear testing)	One each of the following sizes; 19mm, 25mm, 31mm. (Previously used in Accelerated Wear testing)	None of three S.A.V. valves tested were significantly impaired following 240 Mcycles with leakage rates <1.2 mL/sec. One S.A.V. and two C.E.P.B. valves were considered significantly impaired by the end of 260 Mcycles with leakage rates > 33.3 mL/sec (2 L/min). No wireform fractures or significant deformations occurred in any of the test or reference aortic valves. In summary, the S.A.V. aortic valves failed under the typical tissue wear modes expected for tissue valves.
Stress Analysis	Each of the following sizes were evaluated: 19mm, 21mm, 23mm., 25mm, 27mm, 29mm, and 31mm.	Not Applicable	The results demonstrate that the peak local operating stresses are highest in the size 23mm wireform, at 43.62 ksi.
Fatigue Lifetime Determination	Fatigue data from size .031" diameter wire coupled with the stress analyses from the size 23mm wireform.	Not Applicable	The results of the fatigue lifetime determination demonstrate that the worst-case wireform (size 23mm) has a predicted lifetime of ≥ 15 years.
Sewing Ring Integrity	Four each of the following sizes: 19mm, 21mm, 23mm, 25mm, 27mm, 29mm, 31mm.	Not Applicable	The results show the structural integrity of the S.A.V. valve stent components (sewing ring subassembly and Elgiloy/PET band subassembly) are maintained under a loading force up to three times greater than a hypertensive (200 mmHg) load.

9.1.4 Magnetic Resonance Imaging (MRI) Compatibility

Testing of this device in a magnetic field of 1.5, 3.0 and 8.0 Tesla has shown that this device is safe and compatible during MRI (magnetic resonance imaging) procedures.

9.2 Animal Studies

9.2.1. Valve Implantation Studies

A chronic *in vivo* animal implantation study was conducted using Carpentier-Edwards S.A.V. Bioprosthesis Model 2650 valves implanted in a healthy juvenile sheep model. A total of twenty sheep were implanted with the SAV Model 2650 valve in either the aortic or mitral position. A total of eleven animals survived the required implant period of five months: five implanted in the aortic position and six in the mitral position. All eleven animals remained healthy throughout the inlife period. The animals demonstrated no clinical signs indicative of valve related abnormalities over the 6-month (24-week) evaluation period. The general health of the animals, hematology, *in vivo* hemodynamics, and an evaluation of both the animal and valve at the time of explant demonstrated that, when properly implanted, the S.A.V. bioprothetic valve was safe and functional after 6 months implant duration.

Parameters evaluated during the study included physical observations, implantation characteristics, cause of death, hematology and blood chemistry measurements (following implant and at explant), hemodynamic evaluations including cardiac output and peak transvalvular gradients (at explant only), explanted valve analysis for calcium and phosphate content, necropsy observations, and histopathological evaluation of selected organs and of the explanted valve and host tissue. In addition, cineangiographic and echo doppler analysis were performed prior to explant. A summary of the study results is provided in **Table 9.2.1-1**.

Table 9.2.1-1: Animal Study Summary

Evaluation Parameter	Summary of Results
Clinical Chemistry and Hematology	Hematology and blood chemistry were within normal limits for the age and size of sheep evaluated.
Hemodynamic Performance	Cardiac outputs and transvalvular pressure gradients appear within the normal limits for the age and size of sheep evaluated. Results from both color doppler and aortography techniques demonstrated valve competency with minor exceptions: mild regurgitant (1+) jets at the leaflet coaptation in sheep 941, 904, and 949. A small perivalvular leak was also observed in sheep 935 and 944. No hemodynamic results were available for sheep 938 due to fibrillation of the left ventricle during doppler or sheep 958.
Histopathology	All surviving animals were sacrificed at approximately twenty four weeks post implant. Selected systemic organs were grossly examined and microscopically evaluated. All organs were observed to be normal, with these exceptions: varying degrees of chronic inflammation in the liver observed in several animals; inflammation in the lung of sheep 935 and 937, and minimal acute inflammation associated with necrosis in the liver of sheep 942. In addition, histopathological evaluations of the explanted valves and host tissue revealed that the hearts in sheep 939, 942, 944, 949 and 958 demonstrated chronic inflammation. Similarly, the valves of all animals showed varying degrees of fibrosis sometimes accompanied by minimal inflammation, mineralization and bone formation. All of these changes are typical responses to the surgical implantation or manipulation of tissue, which is exposed to hemodynamic forces. Neither of these sets of changes was unexpected under these experimental conditions.
Elemental Analysis	Samples of the explanted bioprothetic valve leaflets were evaluated for calcification by measuring calcium (Ca) and phosphate (PO ₄) content. The measured values were not considered significant unless they were greater than 1 ppm. Sheep 939 and 958 showed no gross or histopathological signs of calcium impairment although the concentrations in these leaflets were greater than 1 ppm. Sheep 937 had three small discolorations on one leaflet with the other two appearing normal. None of the sheep that survived the duration of the study suffered any sequelae from the increased calcium concentrations as was evidenced in the histopathology report.
Handling Characteristics	All valves were sewn in with relative ease and observed to have good coaptation and fit within each annulus.

9.2.2 Calcification Mitigation Studies/Subcutaneous Implantation Studies

Two *in vivo* subcutaneous implantation studies in rats and rabbits were performed. Porcine aortic valve tissue exposed to Edwards Lifesciences XenoLogiX™ processes (fixation in glutaraldehyde, processing in a solution containing ethanol and polysorbate 80 [a surfactant], and packaging in glutaraldehyde) were tested against tissue exposed to glutaraldehyde only. Samples were implanted into subcutaneous pockets created in weanling rats approximately 24 to 28 days of age and into juvenile rabbits approximately eight weeks of age. Implant duration ranged from approximately 30 days to 90 days from the date of implantation. After explant, samples were evaluated for x-ray evaluation, histological evaluation, and quantitative elemental analysis. The

results indicate that porcine aortic valve tissues exposed to Edwards XenoLogix™ process show a significant reduction in calcification potential in these animal models when compared to samples that are exposed to a glutaraldehyde fixation process alone. The clinical significance of these studies is unknown. A matrix of the subcutaneous implant studies performed is provided in **Table 9.2.2-1**.

Table 9.2.2-1 Subcutaneous Implant Studies

Study and Test Parameters	Results: Porcine Tissue Exposed to XenoLogix™ Process n = 12 ¹	Results: Porcine Tissue Exposed to Glutaraldehyde-Only n = 12 ¹	Statistical Analysis Results
90-Day Rat Subcutaneous Implant Study			
X-ray evaluation ¹	0.0 ± 0.0	3.0 ± 0.0	p < 0.05
Histological evaluation ²	1.4 ± 1.4	3.7 ± 0.5	p < 0.05
Elemental analysis ³	Calcium: 56 ± 69 Phosphate: 74 ± 89	Calcium: 219 ± 15 Phosphate: 324 ± 38	p < 0.05 p < 0.05
90-Day Rabbit Subcutaneous Implant Study			
X-ray evaluation ¹	1.9 ± 1.2	3.0 ± 0.0	p < 0.05
Histological evaluation ²	1.4 ± 1.4	3.3 ± 0.5	p < 0.05
Elemental analysis ³	Calcium: 102 ± 77 Phosphate: 126 ± 94	Calcium: 250 ± 25 Phosphate: 360 ± 23	p < 0.05 p < 0.05

Notes:

1. Three animals implanted with 4 porcine tissue samples each per study.
2. Explanted tissue is examined by x-ray and graded for degree of calcification: 0 = none; 1 = mild; 2 = moderate; 3 = severe. Statistical analyses between groups performed using the Wilcoxon rank sum test.
3. Explanted tissue is Von Kassa stained and examined histologically for the presence of calcium phosphate: 0 = negative; 1 = minimal; 2 = mild; 3 = moderate; 4 = marked; 5 = severe. Statistical analyses between groups performed using the Wilcoxon rank sum test.
4. Explanted tissue is analyzed for calcium and phosphate content. Results are reported as mg calcium (or phosphate) per g dry tissue weight. Statistical analyses between the groups performed using a two-sided t-test.

9.3 Sterilization

The Model 2650 S.A.V. valve is sterilized in buffered glutaraldehyde solution. After terminal liquid sterilization (TLS), the product is held in quarantine until sterility is verified per process specifications. Requalification of the process is performed at regular intervals.

Resterilization and cleaning of the accessory components (stainless steel sizer/handles) was validated using artificial blood inoculated with *B.stearotherophilus*. A 4.0 to 4.7 log reduction was achieved by the cleaning method. Sterility testing at different temperatures using flash, pre-vacuum, and gravity displacement resulted in spore log reduction ranging from 15.1 to 30.0 depending on the method used.

9.4 Shelf Life

Both packaging and product integrity studies were conducted to ensure that the shelf life for the package and product is maintained for a minimum of four (4) years. Packaging integrity consisted of accelerated aging, whereas product integrity samples underwent real-time aging.

9.4.1 Package Integrity

The integrity of the valve packaging components was evaluated after exposure to the maximum steam sterilization cycles and terminal liquid sterilization process. Package integrity testing consisted of physical (leak and glutaraldehyde packaging solution concentration) and sterility testing before and after exposure to glutaraldehyde in an elevated temperature condition, and after a simulated shipping process. Accelerated aging results simulating 0, 1, and 4 years real-time demonstrated package integrity throughout the 4-year shelf life period. Packaging validation

studies conducted after maximum exposure to the terminal liquid sterilization process demonstrated that this sterilization method does not adversely affect package integrity.

9.4.2 Product Integrity

- Nonbiological Components

Stent components used in the Model 2650 S.A.V. valve were evaluated by functional testing of the individual nonbiological materials after 4 years of real-time storage in glutaraldehyde. Results demonstrate that storage in glutaraldehyde up to 4 years has minimal effect on the properties and functions of the individual non-biological materials used in the S.A.V. valves.

- Biological Tissue

Porcine valve tissue stability and storage solution adequacy were evaluated using three parameters: shrinkage temperature, moisture content, and glutaraldehyde concentration. Tissue samples subjected to real-time aging were evaluated at designated intervals for shrinkage temperature and moisture content. Glutaraldehyde content of the storage solution was determined by glutaraldehyde assay.

The results demonstrated that the tissue shrinkage temperature is stable over time at the recommended storage temperature of 4° to 25°C for a duration exceeding the 4-year shelf life. The effects of storage time on the moisture content were monitored because chemical changes in the tissue could affect the hydration level of the tissue. A gradual decrease in moisture content with time was seen, with a more rapid decline at higher temperatures. Glutaraldehyde assays showed the expected trend of a gradual increase in concentration over time, with a more rapid increase at higher storage temperatures. Acceptable levels of glutaraldehyde concentration were maintained for the 4-year shelf life period in the recommended storage temperature range of 4° to 25°C. These results demonstrate product integrity to 4 years.

10. SUMMARY OF CLINICAL STUDIES

The Carpentier-Edwards S.A.V. Bioprosthesis Model 2650 clinical trials were designed to study the safety and effectiveness of the valve in aortic valve replacement. Patients requiring isolated aortic heart valve replacement were enrolled in two non-randomized, multicenter clinical studies, studies 99-3 and 90-2. The data from both studies were pooled for the analysis. Study 99-3 was a long term, mostly retrospective and partly prospective evaluation of 217 patients implanted with the Carpentier-Edwards S.A.V. at 3 centers between January 1991 and December 1992. Study 90-2 was a mid-term, prospective evaluation of 151 patients implanted with the valve at 3 centers between June 1990 and September 1991. Since 31 patients were included in both studies at one hospital, the total number of patients in the study was 337.

Tables 10-1 and 10-2 present preoperative and operative patient demographics. Table 10-3 presents the implant information by valve size, including the number of patient years. Tables 10-4 and 10-5 present effectiveness outcomes, Functional New York Heart Association (NYHA) Functional Classification data and hemodynamic data results. Note that the clinical studies evaluated the following sizes: 19, 21, 23, 25, 27, 29, and 31 mm. However, the clinical studies did not generate sufficient data to support the safety and effectiveness of sizes 19, 29, 31mm aortic valves.

The safety endpoints captured in the pooled studies were adverse events. The safety results are provided above in **Table 8.1-1**. Effectiveness endpoints were New York Heart Association (NYHA) functional classification and echocardiographic assessments. Preoperative and operative patient demographics are presented below, followed by the effectiveness results.

Table 10-1: Preoperative Patient Demographics

Variable	Category	Study Results (N = 337; 1392.9 total pt-yrs)	
		n	% (n/N) ¹
Age at Implant	Mean	337	70.2 ± 8.5
Gender	Female	138	41.0%
	Male	199	59.0%
NYHA Classification	I	3	0.9%
	II	92	27.3%
	III	197	58.5%
	IV	45	13.4%
Lesion	Stenosis	243	72.1%
	Insufficiency	35	10.4%
	Mixed	46	13.7%
	Malfunctioning prosthesis	13	3.7%

Note:

1. n = number of patients in each category; N = total number of study patients

Table 10-2: Operative Patient Demographics

Variable	Category	Study Results (N=337; 1392.9 total pt-yrs.)	
		n	% (n/N) ¹
Etiology ²	Calcification/degeneration	253	75.1%
	Rheumatic heart disease	39	11.6%
	Congenital abnormalities	35	10.4%
	Other ³	10	3.0%
Concomitant Procedures ²	None	203	60.2%
	CABG ⁴	115	34.1%
	AAA ⁵ repair/revision	10	3.0%
	Mitral valve repair	7	2.1%
	Other ⁶	8	2.4%
Pre-existing Conditions ²	Prior Myocardial Infarction	155	46.0%
	Chronic Lung Disease	126	37.4%
	Congestive Heart Failure	100	30.0%
	Arrhythmias	51	15.1%
	Systemic Hypertension	104	30.9%
Valve Size (mm)	19	14	4.2%
	21	76	22.6%
	23	115	34.1%
	25	89	26.4%
	27	37	11.0%
	29	4	1.2%
	31	2	0.6

Notes:

1. n = number of patients in each category; N = total number of study patients
2. May be more than one per patient
3. Includes previously failed prosthesis, remote endocarditis, and ischemic disease
4. CABG = Coronary Artery Bypass Graft
5. AAA=Ascending Aortic Aneurysm
6. Includes annulus enlargement, myectomy, pacemaker implant, IABP insertion, and aneurysm repair.

**Table 10-3 Number of Patients Implanted and Number of Patient Years by Valve Size
All Patients Implanted, N=337; Cumulative Follow-Up=1392.9 Patient Years**

	19mm	21mm	23mm	25mm	27mm	29mm	31mm	Total
Number of Patients Implanted	14	76	115	89	37	4	2	337
Nuber of Patients Years	66.9	268.2	476.6	416.6	150.7	11.9	2.2	1392.9

Table 10-4: Effectiveness Outcomes, Functional NYHA

NYHA Functional Class	Preoperative Assessment		Postoperative Assessments			
	n/N ¹	%	1 Year		4 to 5 Years	
			n/N	%	n/N	%
I	3/337	0.9%	157/309	50.8%	106/254	41.7%
II	92/337	27.3%	20/309	6.5%	18/254	7.1%
III	197/337	58.5%	2/309	0.6%	2/254	0.8%
IV	45/337	13.4%	0/309	0.0%	1/254	0.4%
Not Available	0	0.0%	130/309	42.1%	128/254	50.4%

Note:

1. n = number of patients in each category; N = total number of study patients

**Table 10-5: Pooled Studies: Effectiveness Outcomes, Hemodynamic Results¹
(Results reported for all patients evaluated following discharge)**

Hemodynamic Parameter	Results By Valve Size ¹						
	19mm	21mm	23mm	25mm	27mm	29mm	31mm
Discharge (n = 122)							
Mean gradient ²	N = 2	N = 29	N = 39	N = 32	N = 13	N = 2	N = 2
• mean ± sd	13.5 ± 12.0	12.6 ± 5.0	12.0 ± 5.5	10.4 ± 5.0	8.0 ± 5.2	5.1 ± 2.7	5.0 ± 2.5
• min, max	5, 22	4.9, 25	2.1, 35	3.1, 26	3, 23	3.2, 7.0	3.2, 6.7
EOA ³	N = 2	N = 29	N = 38	N = 30	N = 11	N = 2	N = 2
• mean ± sd	0.56 ± .08	1.4 ± 0.47	1.58 ± .83	1.92 ± 0.65	2.01 ± 0.68	3.04 ± 1.2	2.2 ± 0.88
• min, max	0.51, 0.62	0.46, 2.89	0.80, 6.0	0.91, 3.80	1.00, 3.16	2.2, 3.89	1.56, 2.81
Regurgitation ⁴	N = 3	N = 32	N = 40	N = 31	N = 13	N = 2	N = 2
0	3 (100.0%)	26 981.3%	35 (87.5%)	25 (80.6%)	13 (100.0%)	1 (50.0%)	1 (50.0%)
1+	0 (0.0%)	5 (15.6%)	4 (10.0%)	2 (6.5%)	0 (0.0%)	1 (50.0%)	0 (0.0%)
2+	0 (0.0%)	1 (3.1%)	1 (2.5%)	2 (6.5%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
3+	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4+	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not available	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
1 Year (n = 115)							
Mean gradient ²	N = 4	N = 27	N = 37	N = 29	N = 12	N = 2	N = 1
• mean ± sd	17.3 ± 2.6	12.7 ± 4.2	10.5 ± 4.3	11.3 ± 5.5	8.3 ± 3.3	4.2 ± 1.1	5.5 ± 0.0
• min, max	15, 21	4.6, 21.9	2.7, 24.5	3.7, 26.0	3.2, 15.2	3.4, 5.0	5.5, 5.5
EOA ³	N = 4	N = 28	N = 35	N = 29	N = 12	N = 2	N = 1
• mean ± sd	0.75 ± 0.21	1.3 ± 0.4	1.5 ± 0.4	1.7 ± 0.5	1.8 ± 0.6	2.3 ± 0.7	1.5 ± 0.0
• min, max	0.44, 0.92	0.80, 2.40	0.80, 2.58	0.8, 2.7	1.1, 3.2	1.8, 2.8	1.5, 1.5
Regurgitation ⁴	N = 4	N = 30	N = 35	N = 28	N = 12	N = 2	N = 1
0	4 (100.0%)	26 (86.7%)	30 (85.7%)	23 (82.1%)	10 (83.3%)	2 (100.0%)	1 (100.0%)
1+	0 (0.0%)	3 (10.0%)	2 (5.7%)	5 (17.9%)	2 (16.7%)	0 (0.0%)	0 (0.0%)
2+	0 (0.0%)	1 (3.3%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3+	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4+	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not available	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Notes:

- Hemodynamic evaluations were performed using transthoracic echocardiography (TTE).
- Mean gradient in mm Hg.
- EOA: Effective Orifice Area, cm²
- Regurgitation: 0 = none; 1+ = trivial; 2+ = mild; 3+ = moderate; 4+ = severe

10.1 Description of Patients and Analysis for Gender Bias

A gender bias was not found in the Edwards Lifesciences clinical studies.

Of the 337 patients followed in the pooled clinical studies, 59.1% were male and 41.0% were female. This gender distribution is consistent with the incidence of patients presenting for aortic valve replacement in the U.S. The log-rank test was used to compare all valve related adverse event outcomes by gender; there was no significant difference. The rank-sum test was used to compare NYHA improvement; there was no significant difference.

11. CONCLUSIONS DRAWN FROM STUDIES

The results from pre-clinical laboratory studies performed on the Carpentier-Edwards S.A.V. Bioprosthesis Model 2650 for biocompatibility, hydrodynamic performance and structural integrity demonstrate that this device is suitable for long-term implant.

The animal studies show that the Carpentier-Edwards S.A.V. Bioprosthesis Model 2650 is safe for valve replacement.

The preclinical and clinical studies submitted in the PMA application provide reasonable assurance that the Carpentier-Edwards S.A.V. Bioprosthesis Model 2650, available in sizes 21, 23, 25, and 27mm, is safe and effective for the replacement of native or prosthetic aortic valves when used according to the approved labeling.

12. PANEL RECOMMENDATIONS

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 Systems Device Panel, a FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

13. FDA DECISION

The applicant's manufacturing and control facilities were inspected and the facilities were found to be in compliance with the Quality System Regulation (QSR)(21 CFR Part 820).

FDA issued an approval on June 24, 2002.

14. APPROVAL SPECIFICATIONS

Directions for use: See final approved labeling (Instructions for Use)

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

Post-approval Requirements and Restrictions: See Approval Order.