SUMMARY OF SAFETY AND EFFECTIVENESS DATA

1. General Information

Device Generic Name:	Replacement Heart Valve
Device Trade Name(s):	Epic Valve aortic sizes 21, 23, 25, 27, and 29 mm; mitral sizes 27, 29, 31, and 33 mm Epic™ Supra Valve aortic sizes 19, 21, 23, 25, and 27 mm
Applicant's Name and Address:	St. Jude Medical, Inc. One Lillehei Plaza St. Paul, MN 55117
PMA Application number:	P040021/S004
Date of Notice of Approval to the Applicant:	November 15, 2007

The original PMA application (P040021) for the Biocor™ Heart Valve was approved on August 05, 2005. Information from the original application is applicable to the current supplemental application for the Epic™ and Epic™ Supra Heart Valves, and is incorporated by reference. Please refer to the SSED via the CDRH website at http://www.fda.gov/cdrh/pmapage.html. Written requests for copies can be obtained from the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852 under Docket #05M-0359.

2. Indications for Use

The Epic valve is indicated for patients requiring replacement of a diseased, damaged, or malfunctioning native aortic and/or mitral heart valve. It may also be used as a replacement for a previously implanted aortic and/or mitral prosthetic heart valve.

The Epic Supra valve is indicated for patients requiring replacement of a diseased, damaged, or malfunctioning native aortic heart valve. It may also be used as a replacement for a previously implanted aortic prosthetic heart valve.

3. Device Description

3.1 Epic and Epic Supra Valve

The Epic™ valve and the Epic™ Supra valve are bioprosthetic heart valves manufactured from select porcine aortic valve cusps. The cusps are carefully matched for optimum leaflet coaptation and hemodynamics.

Following tissue fixation, the tissue is mounted on the FlexFit™ polyester-covered flexible acetal copolymer stent. The stent is a low-profile design with a scalloped shape.

The stent is covered with knitted polyester fabric. The sewing cuff on Epic standard valves is formed from a braided polyester filler material that is covered by the knitted polyester fabric cover. The sewing cuff on Epic Supra valves is formed by enclosing a molded silicone elastomer within the same knitted polyester fabric as the Epic standard valve. The sewing cuff also contains three suture markers to facilitate valve placement. A stainless steel wire is located under the sewing cuff for radiopacity.

A bovine pericardial tissue strip is attached to the outflow edge of the valve. This strip protects the leaflets as they open and close. The pericardial strip and the porcine valve cusps are preserved and crosslinked in a glutaraldehyde solution. Glutaraldehyde, formaldehyde, and ethanol are used in the valve sterilization process. The valve is attached to a holder and packaged in a sealed jar containing a formaldehyde solution. The Epic and Epic Supra valves are supplied sterile and non-pyrogenic.

Non-clinical testing has demonstrated that the Epic and Epic Supra valves are MR Conditional.

The Epic valve is available for aortic tissue annulus sizes 21mm, 23mm, 25mm, 27mm and 29mm; and mitral tissue annulus sizes 27mm, 29mm, 31mm, and 33mm. Epic standard valves are designed to allow intra-annular placement of the inflow edge of the valve with supra-annular placement of the sewing cuff.

The Epic Supra valve is designed for supra annular placement in the aortic position and is available for tissue annulus sizes 19mm, 21mm, 23mm, 25mm, and 27mm. Epic Supra valves are designed for supra-annular implantation of both the valve and the sewing cuff. The sewing cuff is the only difference between the Epic valve and the Epic Supra valve.

The Epic and Epic Supra valves are treated with the Linx™ anticalcification process.

4. Contraindications

None known.

5. Warnings and Precautions

The warnings and precautions are provided in the device labeling for the Epic valve and the Epic Supra valve.

6. Alternative Practices and Procedures

The alternative treatments to the Epic valve and the Epic Supra valve include drug therapy or surgical treatments such as annuloplasty or valvuloplasty (with or without the use of implantable materials). If a patient requires replacement of their native or previously implanted prosthetic valve, the alternatives include other commercially available mechanical valves, homografts, or bioprosthetic valves. The choice of replacement valve depends on an assessment of patient factors which include age, preoperative condition, anatomy, and the patient's ability to tolerate long-term anticoagulant therapy.

7. Marketing History

Commercial distribution of the Epic valve outside the U.S. began in 1999, and the valve is currently available in the following countries: Argentina, Austria, Belgium, Brazil, Bulgaria,

Cyprus, Canada, China, Columbia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, India, Ireland, Italy, Korea, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Mexico, Netherlands, Philippines, Poland, Portugal, Saudi Arabia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, and the United Kingdom.

Commercial distribution of the Epic Supra valve outside the U.S. began in 2003, and the valve is currently available in the following countries: Austria, Belgium, Brazil, Bulgaria, Cyprus, Canada, China, Columbia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, India, Ireland, Italy, Korea, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Mexico, Netherlands, Philippines, Poland, Portugal, Saudi Arabia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, and the United Kingdom.

The Epic valve and Epic Supra valve have never been withdrawn from commercial distribution for any reason relating to safety and effectiveness of the device.

8. Adverse Events

The clinical investigation of the Epic valve supports the safety and effectiveness of the Epic valve and the Epic Supra valve. Between January 2003 and March 2006, seven-hundred and sixty-two (762) subjects were implanted with 791 Epic Valve(s) at 19 investigational sites in the United States (U.S.), and three sites in Canada. Five-hundred and fifty-seven (557) subjects received isolated aortic replacement, 176 received isolated mitral replacement, and 29 received replacement of both the aortic and mitral valves. The cumulative follow-up for all subjects was 773.51 patient-years with a mean follow-up of 1.02 patient-years (s.d. = 0.71 patient-years, range 0 – 3.10 patient-years).

Table 1: Observed Adverse Event Rates

All subjects entered into study: N=762, cumulative follow-up=717.4 late patient-years

Adverse Event	Early Events [1] n (%)	Late Events[2] n (% / pt-yr)	Bayesian Posterior mean rate[3]	Freedom From Event 1 Year % [95% CI]
Hemolysis	2 (0.3)	1 (0.1)	0.104	99.6% [98.6%, 99.9%]
Structural Deterioration	0 (0.0)	2 (0.3)	0.324	100.0% [100.0%,100.0%]
Paravalvular Leak	2 (0.3)	11 (1.5)	1.363	98.2% [96.7%, 99.0%]
Embolism	20 (2.6)	18 (2.5)	2.136	94.8% [92.8%, 96.3%]
Valve Thrombosis	1 (0.1)	0 (0.0)	0.014	99.8% [98.9%,100.0%]
Major Bleeding Events – Anticoagulant and/or Antiplatelet Related Hemorrhage	38 (5.0)	13 (1.8)	1.357	93.2% [91.0%, 94.9%]
• *Anticoagulant Related Hemorrhage[4]*	*27(3.5)*	*7 (0.98)*	*0.88*	*95.2% [93.2%, 96.6%]*
Endocarditis	1 (0.1)	9 (1.3)	0.845	98.5% [97.1%, 99.2%]

Reoperation	1 (0.1)	11 (1.5)	1.456	98.3% [96.8%, 99.1%]
Mortality - Valve Related	2 (0.3)	5 (0.7)	0.804	99.2% [98.1%, 99.7%]

1. Early events are those occurring on or before 30 days post-implant. The early adverse event rate (%) is calculated as the number of early adverse events divided by the total number of subjects implanted, times 100.
2. Late events are those occurring 31 days post-implant or thereafter.
3. Bayesian posterior mean are the event rates modeled from a Bayesian hierarchical model.
4. Excludes subjects receiving only antiplatelet therapy.

Potential Adverse Events

Adverse events potentially associated with the use of bioprosthetic heart valves (in alphabetical order) include:

- angina
- cardiac arrhythmias
- endocarditis
- heart failure
- hemolysis
- hemolytic anemia
- hemorrhage, anticoagulant/antiplatelet-related
- leak, transvalvular or paravalvular
- myocardial infarction
- nonstructural dysfunction (entrapment by pannus or suture, inappropriate sizing or positioning, or other)
- prosthesis regurgitation
- stroke
- structural deterioration (calcification, leaflet tear, or other)
- thromboembolism
- valve thrombosis

It is possible that these complications could lead to:

- reoperation
- explantation
- permanent disability
- death

9. Summaries of Non-Clinical Studies

9.1 In-Vitro Pre-Clinical Bench Testing

9.1.1 Biocompatibility

Based on the results of the biocompatibility testing performed, the materials used in the Epic valve and the Epic Supra valve were determined to be biocompatible, non-mutagenic, non-toxic and, therefore, safe for the devices intended use.

Non-Biological Components

The non-biological components of the Epic valve consist of surgical sutures, polyester knitted fabric and yarn, stainless steel wire and an acetal copolymer stent, each of which have a long history of use in cardiovascular implantation devices. The Epic Supra configuration

contains the same materials as described above and also contains a silicone ring within the polyester sewing cuff.

Biocompatibility testing of stent sub-assemblies, containing all non-biological components of the valve, were performed in accordance with the requirements detailed in International Standards Organization 10993-1 and United States Food and Drug Administration General Program Memorandum G95-1. For the non-biological components of the Epic valve and the Epic Supra valve, the tests performed, the test objective and results are provided in Table 2. Carcinogenicity, chronic and reproductive toxicity testing were not conducted since the chemical residual profile of the valve did not indicate that these long-term chronic studies were necessary.

Table 2. Biocompatibility Tests and Results - Non-Biological Components

Test Performed	Objective and Method	Controls	Test Article	Results
Cytotoxicity (ISO Elution Method)	Evaluation of the biocompatibility of test article extract using an *in-vitro* mammalian cell culture test (MEM method).	Negative control: low density polyethylene Positive control: Tin stabilized polyvinyl chloride Reagent control: MEM fluid	Covered stent[1] Silicone ring	**Passed** Only slight (grade 1) cytotoxicity observed for the covered stent. The silicone ring showed no reaction (grade 0)
Sensitization (Maximization Method)	Maximization test in guinea pigs to determine the potential for delayed dermal contact sensitization.	Vehicle controls/ control animals	Covered stent[1]	**Passed** No evidence of sensitization
Irritation / Acute Intracutaneous Reactivity (Rabbit Intracutaneous Reactivity Test)	Evaluation of local dermal irritation or toxic effects of leachables extracted from the test article following intra-cutaneous injection in rabbits.	Reagent control per animal	Covered stent[1] Silicone ring	**Passed** No evidence of significant irritation or toxicity
Acute Systemic Toxicity (USP Mouse Systemic Injection)	Evaluation of acute systemic toxicity of leachables extracted from the test article following a single intravenous or intraperitoneal injection in mice.	Control animals dosed with extract vehicles	Covered stent[1] Silicone ring	**Passed** No mortality or evidence of systemic toxicity

Test Performed	Objective and Method	Controls	Test Article	Results
Sub-Chronic Toxicity	Evaluation of the toxicity of leachables extracted from the test article following intravenous injection into mice.	14 day intravenous injections (clinical observation, body weights, necropsy, organ weights, clinical hematology, histopathology); Control animals dosed with extract vehicle	Covered stent[1]	**Passed** No evidence of systemic toxicity
Genotoxicity (Ames Reverse Mutation)	Evaluation of test article to determine its ability to evoke a mutagenic response in strains of Salmonella typhimurium.	Negative control: extract vehicle; positive control: Dexon, sodium azide, and 2-aminoflourine	Covered stent[1]	**Passed** Non-mutagenic
Implantation (Rabbit Intramuscular Implantation Test)	Evaluation of a test article to local pathological effects on living tissue in rabbit.	2 week muscle implant (macro and microscopic examinations of implant muscle sites); negative control material: USP polyethylene	Uncovered stent[2]	**Passed** Classified as a non-irritant
Hemocompatibility	Determination as to whether leachables extracted from the test article will cause a significant level of hemolysis in blood.	Hemolysis- direct contact with rabbit blood, 1 hour at 37°C exposure	Covered stent[1] Cuff filler Stent wire Silicone ring	**Passed** Non-hemolytic

1. The covered stent tested is a subassembly of the Epic valve which contains the implanted non-biological components of the tissue valve. This sub-assembly consists of an acetal copolymer stent (Celcon® M270) that is covered with polyester tubular cloth that has been fashioned around the stent and also forms the sewing cuff exterior. The sewing cuff is filled with braided polyester cloth. Also, a 316 surgical stainless steel (SST) wire is placed in the cuff for radiographic visualization. These components are secured to the stent using polyamide suture material. The stent sub-assemblies were ethylene oxide sterilized prior to testing.
2. The implantation test was not performed using the entire covered stent assembly. The implantation method required 1 mm X 10 mm test samples for loading into muscle tissues using 16 gauge needles/ stylets. This preparation separated the materials of the stent sub-assembly and consequently only the Celcon® M270 stent material was implanted during this test.

Biological Components

The use of glutaraldehyde-fixed porcine leaflets and bovine pericardium are well established for bioprosthetic heart valves and each has an acceptable biocompatibility profile for this indication. The tissues in the Epic valve and Epic Supra Valve are liquid chemically processed in a similar manner to other commercially available heart valves incorporating animal tissues. A thorough assessment of potential leachables from the Epic valves has been performed which includes a study of extractable residuals during rinsing. The results confirm that the extractable chemical residues from the Epic valves are similar in type and concentration as compared to a clinically approved (U.S.) control valve.

Valve Accessories and Packaging Components

The non-implantable valve accessories and packaging components (valve holders, valve sizers, jar, lid, and lid liner) were subjected to a number of biocompatibility tests as appropriate for these components. All results were found to be acceptable.

9.1.2 Hydrodynamic Performance

The Epic Supra valve is identical to the Epic valve with the exception of the device sewing cuff. All hydrodynamic measurements on the Epic valve were conducted with sealed fixtures which isolates the cuff from the flow areas of the valve. Therefore, the hydrodynamic results summarized in Table 3 support the safe performance of the Epic valve and the Epic Supra valve.

Hydrodynamic performance studies were completed on the Epic valve in accordance with the *ISO 5840, Cardiovascular Implants-Cardiac Valve Prosthesis* (1989). Testing included steady flow pressure drop, pulsatile flow pressure drop, dynamic regurgitation, static leakage, flow visualization and verification of the Bernoulli relationship. Commercially available bioprosthetic heart valves were used as controls.

Table 3. Hydrodynamic Performance Summary

Test Type	Sample Size	Control Size	Results
Steady Flow Pressure Drop	3 each size and type	Aortic: 1 each 21mm and 25mm Mitral: 1 each 29mm and 33mm	Steady flow pressure drop is directly correlated to and consistent with pulsatile flow pressure drop results.
Pulsatile Flow Pressure Drop/EOA	3 each size and type	Aortic: 1 each 21mm and 25mm Mitral: 1 each 29mm and 33mm	Meets requirements in ISO/FDIS: 5840 2005 (E), Cardiovascular implants-Cardiac valve prostheses.
Dynamic Regurgitation	3 each size and type	Aortic: 1 each 21mm and 25mm Mitral: 1 each 29mm and 33mm	Valve maintains complete coaptation and meets requirements in ISO/FDIS: 5840 2005 (E), Cardiovascular implants-Cardiac valve prostheses.
Static Leakage	3 each size and type	Aortic: 1 each 21mm and 25mm Mitral: 1 each 29mm and 33mm	Valve closes completely and maintains complete coaptation under a back pressure of 200mmHg.
Flow Visualization	Aortic: 1 each 21mm and 25mm	N/A	The flow field produced by the Epic valve produces a flow field typical of stented tissue valves. Results indicate that the valve opens efficiently and symmetrically.
Verification of the Bernoulli Relationship	Aortic: 1 each 21mm, 25mm, and 29mm Mitral: 1 each 25, and 29mm	N/A	The Bernoulli equation accurately projects true pressure gradient for the valve.

9.1.3 Structural Performance

Since the Epic Supra valve is identical to the Epic valve, except for the construction of the sewing cuff, all structural performance testing conducted on the Epic valve is applicable to the Epic Supra valve. The one exception is the sewing cuff integrity test, which was conducted on both valve models. The structural performance results presented in Table 4 support the safe performance of the Epic valve and the Epic Supra valve.

Structural performance studies were completed on the Epic. Testing included accelerated wear, dynamic failure mode, fatigue, stent creep, and sewing cuff integrity. The structural performance testing summary is provided in Table 4.

Table 4. Structural Performance Summary

Test Type	Sample Size	Control Size	Results
Accelerated Wear	Aortic: 3 each 21mm, 25mm, and 29mm Mitral: 3 each 25mm, 29mm and 33mm	Aortic: 1 each 21mm and 29mm Mitral: 1 each 25mm and 33mm	All valves functioned normally exhibiting proper opening and closing while maintaining backpressure throughout the test. No failures were observed at 200 million cycles.
Dynamic Failure Mode	Aortic: 1 each 21mm, 25mm, and 29mm Mitral: 1 each 25mm, 29mm and 33mm	Aortic: 1 each 21mm and 29mm Mitral: 1 each 25mm and 33mm	The failure mode observed was excessive regurgitation due to leaflet holes and tears. This is consistent with typical failure modes for tissue valves in this in-vitro test. Failures occurred between 640 million and 1.89 billion cycles. The control valves failed between 300 and 780 million cycles.
Fatigue: Finite Element Analysis	Ten 29mm, 31mm and 33mm stents	N/A	The largest stress observed was 25.9 MPa (3750 psi) for the 29 mm stent.
Fatigue Lifetime Analysis	Ten 29mm, 31mm and 33mm stents	N/A	No failures through 600 million cycles at 5,000 psi load.
Stent Creep	Ten 29mm stents	N/A	All stents recovered within minutes with no signs of creep.
Sewing Cuff Integrity Epic valve	Ten of each size	N/A	All test samples exhibited cuff retention in excess of the minimum device specification.
Sewing Cuff Integrity Epic Supra valve	Three of each size	N/A	All test samples exhibited cuff retention in excess of the minimum device specification.

9.2 Pre-Clinical Animal Studies

Long-term (20 week) animal studies with the Epic valve were performed using the juvenile sheep model to evaluate the safety and effectiveness of the valve design. The animal model consisted of juvenile sheep either male or female that were between three and five months old at the time of implant. The implant position was the mitral valve and the valve size implanted was 25 mm for the test and control valves. Baxter Carpentier-Edwards valves (model 2625) were implanted as control valves.

The study included an evaluation of handling and implant characteristics, animal survival, hemodynamic performance, valve pathology, hematology and mineralization. The results of this study further establish the safety of the Epic valve and the Epic Supra valve.

9.2.1 Handling and Implant Characteristics

Handling and implantation characteristics of the Epic valve were evaluated by the implanting surgeon and were considered comparable to the control valve.

9.2.2 Animal Survival

There was one early death at 4 days post-operative in the test group; however, it was not attributed to valve performance.

9.2.3 Hemodynamic Performance

At the time of explant, all animals were subjected to standard heart (direct) catheterization to obtain hemodynamic measurements. Hemodynamic parameters obtained on all animals were typically within the normal physiologic range.

9.2.4 Valve Pathology

Valve pathology included photographic analysis of the explanted valves. The fibrous tissue on the Epic valve at the time of sampling was mature characterized by minimally activated fibroblasts and well-organized extracellular matrix, primarily collagen. Immature fibrous reaction was seen only infrequently. The pathology results support the safety of the Epic valve and the Epic Supra valve.

9.2.5 Hematology

The blood chemistries for the Epic valve were not different from the control valves and all of the animals tested in this study fell within the reference range for juvenile ovine provided by Marshfield Laboratories (Marshfield, WI) and Nemi C. Jain *Veterinary Hematology* (Fourth Edition). There were no remarkable anomalies or any indication of excessive blood trauma in the blood chemistries in any of the test groups that could be attributed to the prosthetic device.

9.2.6 Mineralization

Mineralization was evaluated by X-ray radiographs of whole valves and quantitative analysis using inductively coupled plasma atomic emission spectroscopy (ICP). Only minimal calcium content was measured in the Epic valve cusps and there was a statistical difference found in cuspal tissue calcification between the Epic valves and the control valves.

9.3 Sterilization

The Epic valve and the Epic Supra valve are sterilized with a multi-component liquid chemical sterilant. Microbial screening studies were conducted with a variety of organisms exposed to the sterilant in a simulated manufacturing sterilization process. The D-values derived from the screening studies showed *Bacillus subtilis* var. *niger* is the most resistant microbial organism to this sterilization process.

Microbial survival studies were conducted in triplicate with tissue utilizing *B. subtilis* as the challenge organism. The D-value obtained from the *B. subtilis* microbial survival study was used to calculate the minimum sterilization time required to meet a minimum Sterility Assurance Level (SAL) of 10^{-6}.

9.4 Magnetic Resonance Imaging (MRI) Compatibility

The Epic valve and the Epic Supra valve have been shown to be MR Conditional when tested using an MR system with a static magnetic field of 3-Tesla or less. Testing has demonstrated that the MRI procedure will present no substantial or increased risk to the patient relative to magnetic field interactions (e.g., migration and/or heating). The MRI procedure should not cause significant image artifacts or distortion.

9.5 Shelf Life

The shelf life for the Epic valve and the Epic Supra valve was validated to ensure that both the package integrity and the product integrity were maintained for 4 years.

9.5.1 Package Integrity

The packaging used for the Epic valve and the Epic Supra valve has been shown to maintain sterility for 4 years. Structural integrity of the package was evaluated after exposure to thermal shock cycling, vibration, drop conditioning and accelerated aging to 4 years. Performance evaluation of the package included vacuum leakage testing, temperature indicator testing and microbial challenge after real-time aging to four years. The results demonstrate that the package integrity is acceptable for a 4-year shelf life.

9.5.2 Product Integrity

Integrity of the finished devices was evaluated after real-time aging to 4 years. The evaluation included shrinkage temperature, collagen content (i.e., collagenase resistance and hydroxyproline content), tissue microstructure, solution concentration, solution pH, effectiveness of the physician's rinse, and hydrodynamic testing. The results demonstrate that the product integrity of the Epic valve and the Epic Supra valve is acceptable for a 4-year shelf life.

10. Summary of Clinical Studies

10.1 Study Design

The clinical investigation of the Epic valve supports the safety and effectiveness of the Epic valve and the Epic Supra valve.

This Epic valve clinical investigation was a multi-center, multi-country, prospective, non-randomized, observational study, without concurrent or matched controls, conducted under a common protocol. Bayesian methods were used for the design and analysis of this study. This statistical methodology provides a framework for "borrowing" historical data from the SJM Biocor™ Valve PMA data.

10.2 Description of Patients

Seven-hundred and sixty-two (762) subjects were implanted with 791 Epic Valve(s) between January 2003 and March 2006 at 19 investigational sites in the United States (U.S.), and three sites in Canada. Five-hundred and fifty-seven (557) subjects received isolated aortic replacement, 176 received isolated mitral replacement, and 29 received replacement of both the aortic and mitral valves. Demographic and baseline data were collected preoperatively. Postoperative data, including blood and echocardiography data were collected at discharge, 6 months, one year, and annually thereafter. All echos were sent to the Echo Core Lab for interpretation. Adverse event data was collected at the time of occurrence or site notification using definitions from Edmunds et al., 1961.

The mean age at implant for all subjects was 73.9 years (s.d. = 9.2 years, range 24-93 years). Preoperatively, 57.4 % of all subjects were NYHA classification III/IV. The cumulative follow-up for all subjects was 773.51 patient-years with a mean follow-up of 1.02 years (s.d. = 0.71 years, range 0 – 3.10 years).

Table 5 presents the number of patients implanted, cumulative follow-up, and mean follow-up for each patient implant group. Tables 6 and 7 present the number of patients implanted and cumulative follow-up by valve size and patient implant group.

Table 5. Patient Numbers, and Cumulative and Late Patient follow-up

All subjects entered into study, N=762

Mean, SD, Min, and Max are represented in "Patient-years"

Implant Position	Number of Subjects	Total Patient-years	Mean	SD	Minimum	Maximum
Cumulative Patient-years						
Isolated Aortic	557	582.13	1.05	0.70	0.00	3.08
Isolated Mitral	176	168.96	0.96	0.73	0.00	3.10
Double	29	22.43	0.77	0.66	0.02	2.01
All Implants	762	773.51	1.02	0.71	0.00	3.10
Late Patient-years*						
Isolated Aortic	474	540.93	1.14	0.61	0.00	3.00
Isolated Mitral	147	156.12	1.06	0.65	0.02	3.01
Double	23	20.34	0.88	0.60	0.02	1.93
All Implants	644	717.40	1.11	0.62	0.00	3.01

* Late patient-years at risk are determined from 31 days post-implant to the censoring event.

1 Edmunds LH, Clark RE, Cohn LH, Grunkemeier GL, Miller CM, Weisel RD. Guidelines for Reporting Morbidity and Mortality after Cardiac Valvular Operations. Ann Thorac Surg 1996;62:932-5.

Table 6. Aortic Patient Numbers and Cumulative Follow-up by Valve Size

All aortic subjects entered into study: N=586

		Numbers of Implants by Valve Size (mm)					
		21	**23**	**25**	**27**	**29**	**Total**
Isolated Aortic	**Number of Subjects**	91	206	191	59	10	557
	Number of Patient-Years	98.32	214.77	199.17	58.08	11.79	582.13
Double*	**Number of Subjects**	10	11	7	1	0	29
	Number of Patient-Years	10.15	7.01	5.22	0.04	0.00	22.43

*Aortic valves from Double Valve Replacement patients.

Table 7. Mitral Patient Numbers and Cumulative Follow-up by Valve Size

All mitral subjects entered into study: N=205

		Numbers of Implants by Valve Size (mm)					
		25	**27**	**29**	**31**	**33**	**Total**
Isolated Mitral	**Number of Subjects**	5	34	70	37	30	176
	Number of Patient-Years	3.62	23.29	68.45	41.76	31.83	168.96
Double*	**Number of Subjects**	4	8	9	6	2	29
	Number of Patient-Years	0.63	7.02	9.63	5.05	0.10	22.43

*Mitral valves from Double Valve Replacement patients.

10.3 Analysis for Gender Bias

Of the 762 subjects implanted with the Epic valve, 56.2% were male (AVR – 61.0%, MVR – 44.3%, and DVR – 34.5%). The gender distribution in this study is consistent with the incidence of patients presenting for valve replacement in the U.S.

Kaplan-Meier analysis and Log-rank test were performed to compare all valve related morbidities and mortality by gender for each implant position. For MVR, males had a slightly higher incidence of paravalvular leak and endocarditis than females. There were no significant differences between males and females for all other valve related morbidity and mortality for each valve position. The rank-sum test was performed for NYHA improvement from preoperative to 1 year. There is no significant difference between genders. It is concluded that the results for valve related adverse events following valve replacement are representative of both men and women.

10.4 Patient Demographics

Table 8 presents the preoperative patient demographics.

Table 8. Preoperative Patient Demographics

All subjects entered into study: N=762

Variable	Isolated Aortic (N=557)	Isolated Mitral (N=176)	Double (N= 29)	All (N=762)
Age	74.4 ± 9.3 (24, 93)	72.1 ± 8.9 (44, 91)	75.9 ± 8.3 (55, 92)	73.9 ± 9.2 (24, 93)
Gender (Male)	61.0%	44.3%	34.5%	56.2%
Preoperative NYHA				
I	9.2%	8.0%	0.0%	8.5%
II	34.6%	30.1%	34.5%	33.6%
III	43.1%	43.2%	34.5%	42.8%
IV	12.6%	18.2%	31.0%	14.6%
Unknown	0.5%	0.6%	0.0%	0.5%

10.5 Results

Quantitative data were collected throughout the study (i.e., NYHA functional classification, echo parameters). Table 9 presents patient NYHA classification at one year follow-up. Tables 10 and 11 present the hemodynamic results at one year follow-up for the Epic aortic and mitral valve replacements.

Table 9: Effectiveness Outcomes, NYHA Functional Classification: 1 year Follow-up*

Subjects with both preoperative and 1 year NYHA measurements, N=460; n_1=number per subgroup

NYHA Class	Isolated Aortic n=353				Isolated Mitral n=93				Double n=14			
	Preoperative		1 Year		Preoperative		1 Year		Preoperative		1 Year	
	n_1	% (n_1/n)	n_1	% (n_1/n)	n_1	% (n_1/n)	n_1	% (n_1/n)	n_1	% (n_1/n)	n_1	% (n_1/n)
I	35	9.9	244	69.1	6	6.5	66	71.0	0	0	12	85.7
II	131	37.4	98	27.8	30	32.3	22	23.7	6	42.9	1	7.1
III	146	41.1	11	3.1	40	43.0	5	5.4	4	28.6	1	7.1
IV	39	11.0	0	0	17	18.3	0	0	4	28.6	0	0
All	353	100.0	353	100.0	93	100.0	93	100.0	14	100.0	14	100.0

*Subjects with both preoperative and one year NYHA measurements available are included in this table.

Table 10: Effectiveness Outcomes at One Year Follow-up Visit, Hemodynamic Results - All Aortic Valves

All aortic subjects entered into study: N=586

Hemodynamic Parameter	21mm	23mm	25mm	27mm	29mm*
Mean Gradient	n= 49	n=120	n=121	n= 36	n= 10
~ Mean ± SD	19.1 ± 8.2	13.9 ± 6.0	12.1 ± 5.1	11.4 ± 4.1	7.5 ± 3.3
~ Min, Max	3.1, 43.5	1.7, 35.0	3.7, 34.3	6.5, 26.3	2.7, 12.7
EOA	n= 46	n=118	n=121	n= 35	n= 10
~ Mean ± SD	1.0 ± 0.3	1.4 ± 0.5	1.5 ± 0.5	1.6 ± 0.4	2.4 ± 1.1
~ Min, Max	0.5, 2.3	0.5, 3.5	0.2, 3.3	0.8, 2.7	1.2, 4.6
Regurgitation	n= 56	n=130	n=128	n= 38	n= 10
~ None	47 (84%)	103 (79%)	92 (72%)	28 (74%)	9 (90%)
~ Trivial	7 (13%)	21 (16%)	29 (23%)	9 (24%)	1 (10%)
~ Mild	2 (4%)	6 (5%)	6 (5%)	1 (3%)	0 (0%)
~ Moderate	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
~ Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
~ Unknown	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*Includes 2 subjects at greater than one year visit
n= number of subjects evaluated
Mean Gradient = pressure drop measured across the valve recorded in mmHg
EOA= calculated effective orifice area measured in cm^2
Regurgitation presented as Count (Percentage)

Table 11: Effectiveness Outcomes at One Year Follow-up Visit, Hemodynamic Results - All Mitral Valves

All mitral subjects entered into study: N=205

Hemodynamic Parameter	27mm*	29mm	31mm	33mm*
Mean Gradient	n= 30	n= 41	n= 26	n= 24
~ Mean ± SD	6.1 ± 2.9	5.5 ± 1.7	4.8 ± 1.4	4.1 ± 1.6
~ Min, Max	2.7, 14.0	2.9, 10.0	2.6, 8.3	1.5, 7.9
EOA	n= 16	n= 26	n= 15	n= 22
~ Mean ± SD	1.4 ± 0.7	1.5 ± 0.5	1.6 ± 0.3	1.5 ± 0.3
~ Min, Max	0.6, 3.1	0.6, 2.8	1.1, 2.4	1.1, 2.2
Regurgitation	n= 30	n= 45	n= 28	n= 25
~ None	30 (100%)	41 (91%)	23 (82%)	23 (92%)
~ Trivial	0 (0%)	1 (2%)	0 (0%)	1 (4%)
~ Mild	0 (0%)	3 (7%)	5 (18%)	0 (0%)
~ Moderate	0 (0%)	0 (0%)	0 (0%)	1 (4%)
~ Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)
~ Unknown	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*Includes 4 (27mm) and 6 (33mm) subjects at greater than one year visit.
n= number of subjects evaluated
Mean Gradient = pressure drop measured across the valve recorded in mmHg
EOA= calculated effective orifice area measured in cm^2
Regurgitation presented as Count (Percentage)

11.0 Conclusions Drawn from Studies

The results from the in-vitro pre-clinical studies performed for biocompatibility, hydrodynamic performance and structural performance demonstrate that the Epic valve and the Epic Supra valve are safe and effective and therefore, suitable for long-term implant.

The in-vivo animal studies in sheep demonstrate the Epic valve and the Epic Supra valve are safe for valve replacement.

The clinical results demonstrate that the Epic valve and Epic Supra valve are safe and effective for their intended use.

12.0 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.

13.0 FDA Decision

FDA issued an approval order on November 15, 2007. The applicant's manufacturing facility was inspected and found to be in compliance with the Quality System Regulation (21 CFR 820).

The FDA recommends approval of the SJM Epic Valve Epic Valve aortic sizes 21, 23, 25, 27, and 29 mm; mitral sizes 27, 29, 31, and 33 mm and SJM Epic Supra Valve aortic valve sizes 19, 21, 23, 25, and 27 mm for which there are adequate data.

14.0 Approval Specifications

Instructions for Use: See the labeling

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse events in the labeling.

Postapproval Requirements: See approval order.