SUMMARY of SAFETY and EFFECTIVENESS DATA

St. Jude Medical, Inc. Toronto SPV® Valve

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1. General Information

Device Generic Name: ..... Replacement Heart Valve

Device Trade Name: ..... Toronto SPV® valve

Applicant's Name and Address: ..... St. Jude Medical, Inc.
One Lillehei Plaza
St. Paul, MN 55117

PMA Application Number: P970030

Date of Panel Recommendation: ..... September 16, 1997

Date of Notice of Approval to the Applicant: ..November 24, 1997

2. Indications For Use

The Toronto SPV® valve is indicated for the replacement of malfunctioning native or prosthetic aortic valves.

3. Contraindications

The Toronto SPV® valve is contraindicated for use in patients where the diameter of the aortic annulus is larger than the diameter of the sinotubular junction, or where the diameter of the aortic annulus is more than 10% smaller than the sinotubular junction. Excessive mismatch may cause central incompetence and/or stenosis of the bioprosthesis.

4. Warnings and Precautions

4.1 Warnings

FOR SINGLE USE ONLY

DO NOT RESTERILIZE the valve by any method. Exposure of the valve and container to irradiation, steam, ethylene oxide or other chemical sterilants will render the valve unfit for use.

Warning: Accelerated deterioration due to calcific degeneration of bioprostheses may occur in:

- children, adolescents, or young adults;
- patients with altered calcium metabolism (e.g., chronic renal failure, hyperparathyroidism).

4.2 Precautions

Implanting physicians must be familiar with the techniques for implanting an unstented bioprosthesis. These techniques are similar to those required for allograft implantation.

In vitro testing of the Toronto SPV® valve has only been performed in a less compliant simulated aorta comparable to the aorta of a middle aged or older patient. Data from clinical or *in vitro* testing are not available from a more compliant simulated aorta comparable to the aorta of a younger patient.

4.2.1 Precautions Prior to Use

Do not use the Toronto SPV® valve:

- if the tamper-evident seal is broken;
- if the glutaraldehyde storage solution does not completely cover the valve;
- if the valve has been exposed to freezing or has had prolonged exposure to heat as indicated by the temperature indicators provided in the packaging (see section 10 How Supplied);
- if the valve is damaged.

4.2.2 Precautions During Use

- Do not expose the valve to solutions other than the storage solution in which it was shipped, the sterile isotonic saline solution used during the rinsing procedure, or the sterile isotonic saline used to irrigate the valve.
- Do not allow the valve tissue to dry. Continuous submersion or irrigation is required (see section 11 Directions for Use).
- Do not add antibiotics to either the storage or the rinse solution. Do not apply antibiotics to the valve.
- Do not lacerate the valve tissue. If a valve is damaged, the valve must be explanted and replaced.
- Do not evert the valve. Eversion will damage valve tissue.
- Passage of a catheter through any bioprosthesis may damage the valve and is, therefore, not recommended.

5. Device Description

The Toronto SPV® valve is a stentless subcoronary porcine aortic valve preserved in 0.5% glutaraldehyde. It is comprised of only the valve cusps and enough aortic tissue to support the commissures and leaflets. The inflow edge is trimmed to form a flat plane perpendicular to the axis of the valve. The aortic wall tissue on the outflow edge is scalloped, with all three sinuses removed, following the natural contour of the leaflet attachments. The outer surface is covered with a single layer of polyester fabric. The Toronto SPV® valve is suspended on a holder and tripod assembly within a sealed jar containing a 0.5% glutaraldehyde packing solution. The Toronto SPV® valve is supplied sterile and non-pyrogenic, and is available in tissue annulus sizes 21 mm, 23 mm, 25 mm, 27 mm and 29 mm.

Use only St. Jude Medical, Inc. SPA 300 sizers and accessories to size the Toronto SPV® valve.

6. Alternative Practices and Procedures

The Toronto SPV® valve is a replacement for a diseased, damaged, or malfunctioning native or prosthetic aortic heart valve. The alternatives for aortic valve replacement are commercially available mechanical valves, homografts, or stented 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.

Other forms of treatment may include the use of cardiac drug therapy.

7. Marketing History

Marketing of the Toronto SPV® valve outside the U.S. began in 1991, and the valve is currently available in the following countries: Austria, Belgium, Canada, China, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Liechtenstein, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, and the United Kingdom. The Toronto SPV® valve has not been withdrawn from marketing for any reason relating to the safety and/or effectiveness of the device.

8. Adverse Events

A total of 577 Toronto SPV® valves were implanted in the subcoronary position in 577 patients at 12 centers. All 577 patients were included in the adverse event evaluation. The cumulative follow-up was 1325 years with an median follow-up of 2.1 years (range 0 to 6.0 years).

8.1 Observed Adverse Events

Table 1: Observed Adverse Events

All patients implanted: N=577,Cumulative Follow-up=1325 patient-years (pt-yr.)

	Early Events[1] %(N)	Late Events[2] %/pt-yr. (N)	Actuarial Freedom by Kaplan-Meier [95% CI] 1 Year	3 Year	5 Year
Death (all Causes)	2.8% (16)	2.3%/pt-yr (29)	94% [92%, 96%]	91%[89%, 94%]	89% [84%, 94%]
Death (related/unexplained)	0.3% (2)	0.5%/pt-yr (7)	99% [98%,99.5%]	98% [97%, 99%]	98% [97%, 99.5%]
Thromboembolism	1.4% (8)	1.5%/pt-yr (19)	97%[95%, 98%]	94% [92%,97%]	94% [91%, 97%]
Permanent Neuro Events	1.0% (6)	0.5%/pt-yr (6)			
Transient Neurological Events	0.3% (2)	0.9%/pt-yr (11)			
Peripheral Arterial Events	0.0% (0)	0.2%/pt-yr (2)			99.4% [98%, 100%]
Valvular Thrombosis	0.0% (0)	0.0%/pt-yr (0)	100%	100%	100%
Structural Deterioration	0.0% (0)	0.0%/pt-yr (0)	100%	100%	100%
Nonstructural Dysfunction	0.0% (0)	0.0%/pt-yr (0)	100%	100%	100%
Anticoag-Related Hemorrhage	0.0% (0)	0.3%/pt-yr (4)	99%[99%,100%]	99% [98%, 100%]	99% [98%, 100%]
Paravalvular Leak	1.6% (9)	0.6%/pt-yr (8)	97% [96%, 99%]	97% [95%, 98%]	96% [95%, 98%]
Endocarditis	0.2% (1)	0.4%/pt-yr (5)	99% [98%,99.9%]	99% [98%,99.8%]	99% [98%, 99.8%]
Hemolysis	0.0% (0)	0.0%/pt-yr (0)	100%	100%	100%
Reoperation (including Explant)	0.2% (1)	0.3%/pt-yr (4)	99% [99%, 100%]	99% [98%, 99.9]	99% [98%, 99.9%]
Explant	0.2% (1)	0.3%/pt-yr (4)	99% [99%,100%]	99% [98%, 10%]	99% [98%, 99.9%]

[1] *Early events are those occurring on or before 30 days post-implant*

[2] *Late events are those occurring 31 days post-implant or thereafter.*

8.2 Potential Adverse Events

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

- cardiac dysrhythmias;
- death;
- endocarditis;
- hemolysis;
- hemorrhage, anticoagulant/antiplatelet-related;
- leak, transvalvular or paravalvular;
- nonstructural dysfunction (pannus, suture, inappropriate sizing, or other);
- structural deterioration (calcification, leaflet tear, or other);
- thromboembolism;
- valve thrombosis.

9. Summaries of Preclinical Studies

9.1 Bench Testing

9.1.1 Biocompatibility

All component materials used in the Toronto SPV® valve - surgical suture, polyester fabric, and glutaraldehyde tanned porcine heart valve tissue - have a long history of use in cardiovascular applications. The suture material is a standard surgical suture and meets all USP Class VI requirements. In addition, endotoxin and cytotoxicity testing were conducted on the suture material to ensure acceptable endotoxin levels. The polyester fabric is the Weavenit™ Graft product purchased from Meadox Medicals. Meadox has performed complete biocompatibility testing on this material that meets all international requirements. The glutaraldehyde tanned porcine tissue has an extensive clinical history with heart valves and related products and has demonstrated freedom from complications related to biocompatibility. The Toronto SPV® valve components and accessories including sizers, holders and handles were subjected to acute systemic toxicity, intracutaneous toxicity, cytotoxicity and muscle implantation testing. All test results were found acceptable.

9.1.2 Hydrodynamic Performance

Hydrodynamic performance tests were conducted on Toronto SPV® valves mounted in compliant test chambers. Hydrodynamic testing used test chambers with a compliance of 4% ± 1% as measured at a transmural dP/dt of +400± 100 mmHg/sec over a pressure range from 40 to 200 mm Hg. ***Three of each size 21, 23, 25, 27, and 29 mm Toronto SPV® valves were evaluated. One 19 mm and one 29 mm commercially available aortic valves were used as controls.***

9.1.2.1 Steady State Forward Flow

Steady state forward flow testing was performed to examine pressure drop as a function of flow rate over the range of 5 to 30 L/min. The results of these tests revealed that the pressure drop for the 19 mm Toronto SPV® valve is comparable to the 19 mm control valve, while the 29 mm Toronto SPV® valve has significantly lower pressure drop at all flow rates in comparison to the equivalent size control valve.

9.1.2.2 Pulsatile Flow Pressure Drop and Regurgitation

Pulsatile flow pressure drop and regurgitation, including leakage, was evaluated with a pneumatic pulser and diaphragm pump to simulate the left ventricle. Pulsatile flow of compressed air and vacuum were applied alternately to a diaphragm the pneumatic pulser to provide pulse rates between 25 to 200 beat/min, stroke volume from 0 to 100 ml, with a variable ratio of systole to diastole.

Pressure drops across the test valves were obtained by integrating the ventricular and aortic pressure traces during systole. The mean flow rate and root mean square flow rate were also measured over the same time interval. The measurements were conducted at a pulse rate of 70 beats/min and nominal cardiac outputs of 2.4, 3.8, 5.1, and 6 3 L/min.

Leakage and total regurgitant volumes of the test valves were obtained by integrating the flow trace during diastole with nominal mean aortic pressures (averaged over the entire cycle) of 75, 95, 125, and 155 mm Hg. The pulse rate was 70 beats/min with a nominal cardiac output of 5.1 L/m.

Pressure drops were lower and Effective Orifice Area (EOA) values were larger for both the 19 mm and 29 mm Toronto SPV® valves as compared to the pulsatile results for the corresponding control valves. The closing reflux portion of regurgitation for both the 19 mm and 29 mm

control valves. The closing reflux portion of regurgitation for both the 19 mm and 29 mm Toronto SPV® valves are comparable to the corresponding control valve results. However, leakage for the Toronto SPV® valves was lower when compared to the results for the control valves.

9.1.2.3 Flow Visualization

Color Doppler flow mapping (CDFM) was used to qualitatively visualize the flow fields downstream of a 29 mm Toronto SPV® valve. The studies were conducted at a heart rate of 70 beats/min, systolic duration of approximately 280 msec, mean aortic pressure of 100 mm Hg, and cardiac outputs of 3.0 and 5.0 L/min.

The CDFM results showed that the Toronto SPV® valve portrayed acceptable leaflet motion when evaluated under the established test conditions. The flow through the valve was observed to be relatively uniform, with a peak velocity of 1.5 m/sec (at the cardiac output of 5.0 L/Min) located distal to the leaflet tips. No leakage flow was noted after the valve had completely closed; however, a small amount of reverse flow was seen around the valve fixture.

9.1.2.4 Transvalvular Pressure Loss

Verification of the Bernoulli relationship was performed with Doppler ultrasound. This method provided a non-invasive means for evaluating the transvalvular pressure loss. One of each size 19, 23, and 29 mm Toronto SPV® valves were studied. Doppler velocity measurements of four cardiac outputs between 2 to 10 L/min were conducted. Two sets of measurements were performed to acquire data on peak velocities and mean velocities separately. Continuous wave (CW) mode was used for all the measurements distal to the valve to detect the maximum fluid velocities (V_d). The velocities proximal to the valve (V_p) were determined by pulse Doppler at 10 mm upstream of the valve. Pressure measurements were also conducted simultaneously to determine the peak or mean pressure drop. The upstream pressure was measured at the same location where Doppler velocity measurements were taken (10 mm upstream of the valve). For measurement of downstream pressure, the catheter was moved to locate the minimum pressure downstream of the valve which resulted in the maximum pressure drop. The results showed that the simplified Bernoulli equation ($\Delta P = 4 \times (V_d^2 - V_p^2)$) can be applied to estimate peak transvalvular pressure drop from Doppler velocity measurements with high confidence.

9.1.3 Structural Performance

9.1.3.1 Accelerated Life Testing

Structural performance of the Toronto SPV® valve was evaluated using accelerated life testing. The test chamber compliance was 4% $\pm$ 1% per 40 mmHg pressure difference from 40 to 200 mmHg. Six of the largest Toronto SPV® valves (29 mm aortic) and three of all other valve sizes were tested for an equivalent cycling duration of at least five years (200 x10^6 cycles). Three 29 mm Carpentier-Edwards valves were also tested as reference valves.

Test valves were cycled at a rate of 1000 cycles/minute with a minimum transvalvular pressure of 100 ± 10 mm Hg. Each valve was examined every 20 million cycles for any macroscopic defects (holes, tears, or coaptation problems). At the same time, the transvalvular pressures were measured and adjusted if necessary and the valve opening and closing was verified and photographed with the aid of a strobe light. In addition, at the beginning and at approximately 60, 140 and 200 x10^6 elapsed cycles the hydrodynamic performance of each valve was characterized by pulsatile flow pressure drop and the valvular regurgitation measurements. The compliance of the valve/test chamber compliance was also assessed at these points to verify test stability.

The results of this study showed that the Toronto SPV® valve prosthesis can sustain 200 million cycles of operation in an accelerated life tester without excessive deterioration. The wear results for the Toronto SPV® valve compare favorably to the commercially available control valves. Of the twenty-seven Toronto SPV® valves used in the durability test, only five valves showed any observable wear after 200 million elapsed cycles. None of the five valves with observable wear had to be removed from the test as a result of functional incompetence. Regurgitation volumes and pressure drop data remained constant (values were within the measurable error of the test system). In comparison, one of the control valves had to be removed from the test after 138.5 million cycles due to the development of a large hole resulting in the inability to maintain the required test system back pressure.

Periodic unaided visual examination of valves every 20 million cycles did not reveal any noticeable defects other than the large hole observed at 138.5 million with one of the reference valves. Minor defects in the Toronto SPV® valve observed at completion of accelerated testing were most likely not detected during periodic visual examinations due to lack of magnification and visual access restrictions with the valves mounted in the compliant chambers. The compliance measurements of the valve/chamber combinations show that the valves remain relatively stable over the duration of the accelerated life test.

9.1.3.2 Hydrodynamic Studies

The results of the hydrodynamic studies at the completion of the 200 million cycles showed that the Toronto SPV® valves had low pressure drops and close properly without excessive leakage even when subjected to high back pressures. The stentless valves tested showed lower leakage and regurgitation than the commercially available control valves tested. The pulsatile flow pressure drop values were very similar, with the Toronto SPV® valve typically producing a lower pressure drop than the control valve.

9.2 Animal Testing

Aortic valve replacement was accomplished in young sheep (35-65 kg, 6-13 months old) without technical difficulty (e.g., paravalvular leak; impairment of coronary ostia; misplaced sutures); however, aortotomy fibrosis (i.e., supravalvular stenosis) limited the utility of this animal model for the assessment of hemodynamic performance. Fibrosis occurring at the aortotomy site and concomitant growth of the native aorta resulted in significant narrowing of the aorta and the development of cardiomegaly as well as pulmonary and hepatic congestion. Despite the limitations of this model, five (5) of the eight (8) Toronto SPV® valves demonstrated an effective oriface area greater than 1.0 cm^2 and the assessment of valve-related pathology was accomplished.

Twelve (12) Toronto SPV® valves (size range 18 - 23 mm diameter) and five (5) control valves (commercially available stented porcine aortic valves, 20 or 21 mm diameter), were implanted for 21 weeks (range: 12 days to 21 weeks) and 20 weeks (range: 8.5 to 20 weeks), respectively. Eight valve-related deaths occurred in the Toronto SPV® study group secondary to endocarditis (N=1@12 days), congestive heart failure/aortic insufficiency (N=1 @15 weeks), stenosis (calcification) (N=4 @ 79 days, 19 weeks, 3 months, 4 months) and stenosis (aortotomy fibrosis) (N=2 @ 49 days; 19 weeks). Two valve-related deaths were reported in the control group secondary to stenosis (fibrous sheath formation) following 8.5 and 14 weeks of implantation.

The explant pathology findings demonstrated differences between the Toronto SPV® and the commercially available control valves. Leaflet calcification was the predominant finding in the Toronto SPV® series, while fibrous sheath formation occurred on the control valve leaflets. Quantitative calcium studies demonstrated greater mineralization within leaflets from the Toronto SPV series as compared to the control valve explants. Stenosis resulting from either leaflet

calcification (Toronto SPV®) or fibrous sheath formation (control valve) contributed to the development of cardiomegaly and passive organ congestion in both study groups. Clinical studies will be necessary to assess the effect of leaflet calcification on the long-term hemodynamic performance of the Toronto SPV®. bioprosthesis.

9.3 Shelf life

The packaging system for the Toronto SPV® valve was tested using both real time and accelerated aging studies. Tissue valve functionality was demonstrated through real time aging studies.

9.3.1 Real Time and Accelerated Aging of Valve Package

Pre-sterilized valve packages were aseptically filled with culture media and closed. Prior to accelerate aging at a contract test laboratory, the media filled valve packages were shipped cross country for a total of three air shipments and exposed to temperature fluctuation cycles between 2° and 45° C to simulate transit stresses. These valve packages were then exposed to accelerated age cycles to simulate three years at ambient storage, pressure excursions (100 cycles), and microbial challenge testing. The packages were then incubated and evaluated for sterility. Testing demonstrated that the valve package system would provide an effective barrier to maintain the sterility of the Toronto SPV® valve.

This package system was also evaluated over a 4 year period. Pre-sterilized packages were aseptically filled with phosphate buffer and closed. These packages were then preconditioned with temperature excursions and mechanical shaking and stored at ambient conditions for a 4 year period. The content of the valve jars was tested for sterility at 6 month intervals throughout the 4 year storage time. Results demonstrated that the package system used for the Toronto SPV® valve is capable of maintaining a sterile barrier for four years.

9.3.2 Real Time Aging of Tissue Valve

Sixty tissue valves packaged within the final package system were preconditioned by cross country shipment, exposure to temperature fluctuations (2° and 45° C), and drop tested per Mil Std 810C. The valves were stored at ambient conditions for a total of 4 years. Testing was conducted at baseline and at 6 month intervals. Shrink temperature testing, pulse duplication testing, steady state flow testing, and residual glutaraldehyde assays were conducted to evaluate the tissue integrity and valve functionality over this 4 year period. Results revealed that valves remain fully functional following four years of storage, therefore, expiration dating for the Toronto SPV® valve was established for four years.

9.4 Sterilization

The Toronto SPV® valve is sterilized with a multi-component liquid chemical sterilant. Microbial survival studies were conducted in triplicate with a variety of organisms exposed to the sterilant in a simulated manufacturing sterilization process.

The survival curves generated showed *B. subtilis* var. *niger* spores are the most resistant microbial organism to this sterilization process. The D-value obtained from the *B. subtilis* microbial survival study was used to calculate the sterilization assurance level (SAL) for the minimum sterilization time. The multi component sterilization process produces a satisfactory SAL exceeding the required sterility assurance level of 10^{-6}.

10. Summary of Clinical Studies

The clinical performance of the Toronto SPV® valve was evaluated in a prospective, non-randomized, multicenter international study with patient follow-up out to five years.

10.1 Objectives

This trial compared the implantation and short- and mid-term performance of the aortic Toronto SPV® valve with a non-concurrent, historical control based on selected hemodynamic parameters, morbidity, and mortality.

10.2 Methods

Patients requiring isolated aortic heart valve replacement were enrolled from 1991 to 1997 at 12 US, Canadian, and British centers. After the collection of preoperative NYHA classification and blood data, hemodynamic (by echocardiography), NYHA classification, and blood data were obtained at 3-6 months postoperative, and annually thereafter. Patients were monitored throughout the postoperative period for possible adverse events. Results were compared to FDA-selected literature control publications.

10.3 Description of Patients

The cohort included 577 patients (387 men, 190 women), aged from 33 to 93 years (mean of 66 years). Patients were evaluated preoperatively, within 30 days post-operatively, at 3 to 6 months, and annually. Total follow-up was 1325 patient-years (mean 2.0 years, SD 1.4 years, range 0 to 6.0 years).

Table 2. Preoperative Patient Characteristics

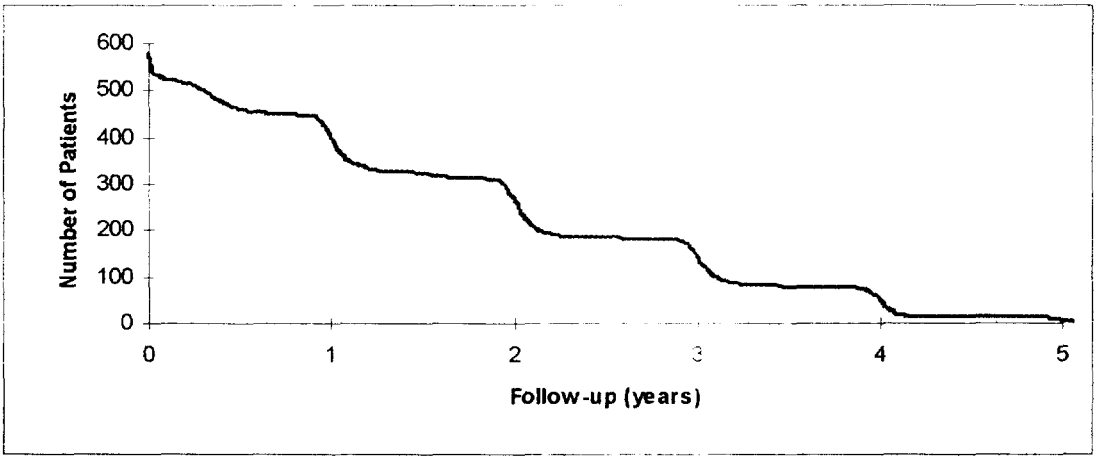
All patients implanted: N=577

Age (mean ±SD), [min., max.], (N)	65.6 ± 10.9, [33.3, 93.4], (577)
Gender (% male/% female)	67%/33%
Etiology and pathology (n/N, %)	
- calcification	70%, 404/577
- congenital	30%, 173/577
- rheumatic fever	13% 76/577
- endocarditis	2%, 9/577
- prosthetic failure	2%, 14/577
- other	2%, 13/577
- unknown	3%, 16/577

Figure 1 shows the number of patients implanted *versus* duration of follow-up in the graphic with a breakdown by valve size in the associated data array

Figure 1. Number of Patients by Valve Size and Duration of Follow-up

All patients implanted, N=577, 1325 patient-years, median = 2.1 years



Year	0	1	2	3	4	5
21 mm*	21	8	5	3	3	0
23 mm	68	43	24	12	6	1
25 mm	136	100	67	38	9	1
27 mm	193	139	90	52	14	2
29 mm	161	118	83	42	19	2
Total	577	408	269	147	51	6

** 21 mm includes 20, 21 and 22 mm valve sizes*

10.4 Analysis for Gender Bias

Study inclusion and exclusion criteria were designed and the study carried out to avoid gender bias in patient enrollment. Of all patients enrolled, 387 of 577 (67%) were male. This proportion of males is consistent with the male to female incidence of patients presenting for valve replacement in the US and Canada.

Preoperatively, females and males entered with equivalent NYHA functional classification (mean 2.62 and 2.55, respectively). By one year both groups experienced an average improvement of 1.4 functional class levels.

Based on risk factors analyses, the underlying distribution of complications did not vary by gender. Comparing EOA, mean and peak systolic gradient, and cardiac index between females and males after stratifying by valve size, there were no statistically significant difference in hemodynamic performance based on gender. Hence, the results presented in the following analyses are representative for both men and women.

10.5 Results

Table 3 shows the improvement NYHA classification and valvular hemodynamics in patients receiving the Toronto SPV® valve. Table 4 presents complication rates which were equivalent or superior to those seen with similar heart valves described in the literature control publications.

Table 3. NYHA and Hemodynamic Outcomes

All patients implanted: N=577, all values reported as: mean ± SD [min., max.] (Number of values)

Intervall	Preoperative	30 days[1]	3 - 6 months	1st Annual
NYHA Classification	2.6 ± 0.7, [1,4] (565)	1.9 ± 0.5, [1,3] (339)	1.2 ± 0.4, [1,4] (501)	1.1 ± 0.4, [1,4] (445)

Endpoint	30 days[1]	3 - 6 months	1st Annual
Valvular Regurgitation[2]	0.2 ± 0.5 [0+,3+] (519)	0.2 ± 0.6 [0+,4+] (477)	0.2 ± 0.6 [0+,4+] (452)
Mean pressure gradient (mmHg)			
21 mm[3]	12.2 ± 9.7 [2, 42] (17)	9.7 ± 8.4 [2, 37] (15)	10.0 ± 9.0 [1, 34] (13)
23 mm	10.3 ± 6.1 [1, 30] (62)	8.0 ± 5.2 [0, 29] (57)	7.3 ± 4.8 [1, 25] (46)
25 mm	8.3 ± 5.2 [1, 30] (117)	7.0 ± 4.8 [0, 26] (109)	6.4 ± 5.1 [0, 32] (111)
27 mm	8.2 ± 5.5 [0, 43] (173)	5.3 ± 3.4 [0, 16] (162)	5.1 ± 3.1 [1, 14] (155)
29 mm	6.2 ± 3.5 [1, 16] (141)	4.4 ± 2.7 [0, 14] (140)	3.8 ± 2.3 [0, 13] (130)
Effective Orifice Area (cm^2)			
21 mm[3]	1.2 ± 0.6 [0.3, 2.5] (17)	1.3 ± 0.6 [0.5, 2.5] (16)	1.3 ± 0.7 [0.2, 2.6] (14)
23 mm	1.4 ± 0.4 [0.4, 2.2] (61)	1.5 ± 0.5 [0.5, 2.9] (57)	1.5 ± 0.6 [0.4, 4.1] (46)
25 mm	1.6 ± 0.6 [0.6, 4.6] (116)	1.6 ± 0.5 [0.3, 3.2] (108)	1.7 ± 0.5 [0.6, 3.8] (111)
27 mm	1.9 ± 0.6 [0.4, 3.5] (171)	2.0 ± 0.5 [0.9, 3.9] (160)	2.0 ± 0.6 [0.9, 4.9] (156)
29 mm	2.2 ± 0.7 [0.9, 5.9] (139)	2.3 ± 0.7 [1.0, 4.9] (139)	2.5 ± 0.8 [1.0, 5.9] (129)

[1] *Post-operative evaluation conducted at 30-days post-implantation or hospital discharge.*
[2] *Average level of regurgitation (0+ = none, 1+ = trivial, 2+ = mild, 3+ = moderate, 4+ = severe)*
[3] *Data pooled from valve sizes 20 mm, 21 mm, and 22 mm*

Table 4. Comparison of Complication Rates

All patients implanted: N=577, all values reported as: mean ± SD [min., max.] (Number of values)

	Kaplan-Meier Freedom From Event at One Year		Late (> 30 days) Events/Patient-Year	
Adverse Event	Toronto Study Estimate [95% CI][3]	Control[4] (point est. from graphs)	Toronto Study (Estimate + upper 95% CI[5])	2 x OPC[6]
All Deaths	94.2% [92.2, 96.2]	81%, 86±3%, 95±1%	2.3% + 3.3% / PY	--
Thromboembolism	96.5% [94.9, 98.1]	97±1%	1.4% + 2.2% / PY	5.0%/PY
Valve Thrombosis	100% [99.4, 100]	--	0.0% + 0.3% / PY	0.4%/PY
Bleeding[7]	99.4% [98.7, 100]	99±0.5%	0.4% + 0.9% / PY	2.8%/PY
Paravalvular Leak	96.9% [95.4, 98.4]	--	0.8% + 1.4% / PY	2.4%/PY
Endocarditis	99% [98.2, 99.9]	99±0.5%	0.5% + 1.0% / PY	2.4%/PY
Hemolysis	100% [99.4, 100]	--	0.0% + 0.3% / PY	--
Reoperation+Explant	99.4% [98.8, 100]	100±0%	0.0% + 0.7% / PY	--

[1] *Controls presented as mean values obtained from literature control publications -- = no data available*
[2] *Significant regurgitation estimated as moderate or severe by echocardiographic evaluation.*
[3] *95% confidence interval (CI) by Kaplan-Meier method.*
[4] *Control presented as point estimate ± standard error as estimated from literature control publications . -- = no data available*
[5] *Linearized rate = number of patients experiencing late (>30 days post-implant) events per total late patient-years at risk x 100; PY: patient-year. Confidence limits are estimated assuming a binomial distribution.*
[6] *Objective Performance Criteria (OPC) from FDA Replacement Heart Valve Guidance (October 14, 1994). -- = no OPC available.*
[7] *Anticoagulant-Related Hemorrhage.*

10.6 Early Complication Rates

Sixteen (16) deaths occurred in 577 valve implant procedures (2.8%). Twenty (20) patients had major complications which included ten (10) neurologic events, nine (9) trivial or minor valvular

leaks which did not require treatment, and one (1) case each of endocarditis and reoperation. Major complications, death (all causes), or explant occurred in a total of 34 patients (6%, 95% upper CL 7.8%).

10.7 Late Complication Rates

Thromboembolism occurred in 14 patients, one (1) peripherally. Twenty-four (24) patients died for a linearized rate of 2.3% per patient year. The upper 95% confidence limit for all objective performance criteria (OPC) was less than twice the FDA Replacement Heart Valve Guidance OPC rates generated from an extensive review of the literature.

10.8 Analysis of Deaths

Valve related deaths occurred in two (2) patients at 26 and 27 days post-operatively. Late deaths in six (6) patients were attributed to endocarditis in three (3) patients and cerebral embolism in two (2) patients. In one (1) patient the cause was not determined and therefore presumed valve related.

Non-valve related deaths occurred early in three (3) patients where a cause was documented and the valve found intact at autopsy. Late deaths in seven (7) patients were cancer related. Brain stem embolus and suicide were the causes of two (2) late deaths, and a late post-operative hospital death was due to multiple organ failure and coagulopathy.

10.9 Explanted Valves

Four (4) valves required operative replacement for endocarditis. Another four (4) were retrieved at autopsy. Pannus and inflammatory matrix were present at the base of the cusps of three valves, and frank infection in the fourth.

11. Conclusions Drawn from Studies

The results from the preclinical studies performed on Toronto SPV® valve for biocompatibility, hydrodynamic performance (steady state forward flow, pulsatile flow pressure drop and regurgitation, flow visualization and transvalvular pressure loss), and structural performance (accelerated life testing and hydrodynamic studies) suggest that the Toronto SPV® valve is suitable for long-term implant. The Toronto SPV® valve meets specifications for performance and is comparable to existing approved heart valves.

Even though the healing response in the animal model limited the assessment of valve hemodynamics, valve-related pathology was evaluated. The extent of leaflet calcification in this short-term study (implant duration 12 days to 21 weeks) was greater in the Toronto SPV® valve than in the control and is consistent with results reported for other porcine aortic valves. Further clinical studies are necessary to assess the effect of leaflet calcification on the long-term hemodynamic performance of the Toronto SPV® valve

11.1 Safety

Complication rates for the Toronto SPV® valve are similar to those for other similar tissue valves and indicate that the Toronto SPV® valve provides an adequate replacement for malfunctioning aortic valves. An increased incidence of perivalvular leak, which is inherent with the difficult

implantation technique expected for stentless valves, was not seen due in part, to the expertise of the implanting investigators. Operator skill will be addressed in the labeling.

11.2 Effectiveness

During the study period, NYHA functional classification improved in all but three (3) patients and hemodynamic performance was substantially better than that observed in the literature for stented tissue valves. However, the study only provided follow-up data out to 18 months to 2 years, insufficient to assess valve durability. Further clinical study is necessary to evaluate the long-term clinical performance of the valve and to assess failure modes

Therefore, it is reasonable to conclude that the benefits of use of the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the directions for use.

12. Panel Recommendations

On September 16, 1997, the Circulatory System Devices Panel reviewed the data submitted by St. Jude Medical, Inc. The panel recommended approval of the Toronto SPV® valve sizes 21, 23, 25, 27, and 29 mm, with the conditions that:

1. the FDA and the sponsor agree on some method of uniform collection of echocardiographic data;
2. the patient labeling should include a temporary card regarding anticoagulation and the mandate for antibiotic prophylaxis for dental procedures, or other potentially bacteremic procedures;
3. endocarditis, acute infective endocarditis be added to the labeling;
4. the post-marketing analysis should be detailed and include the smaller sizes; and
5. there be mandated physician training.

13. FDA Decision

St. Jude Medical, Inc. submitted amendments to the PMA which satisfactorily addressed the panel's and FDA's concerns. The postapproval conditions agreed to by St. Jude are:

1. Since long-term data for the Toronto SPV® valve are not available, a clinical study must be conducted evaluating a cohort of the IDE study that is composed of at least 400 patients from 7 investigational centers. The study may be completed when 100 patients have attained their 10 year evaluation. The study should be designed to aggressively follow all patients, and assurance should be provided that patients lost-to-follow-up did not introduce significant bias. Complete results of the ongoing study should be reported in the annual reports. All patients should be monitored for safety and effectiveness outcomes according to the protocol from the IDE study, or according to an alternative protocol. The protocol should be submitted as a supplement for FDA review and approval within 45 days from the date of the PMA approval order. The results of your long-term study must be reflected in your labeling when the postapproval study is completed.

2. A post-approval study must be conducted that monitors the new implants in the U.S. patient population for valve-related events causing death, re-operation, or explant. A system must be established that, when these adverse events are identified, any autopsy, operative, pathology, or clinical reports indicating the cause of the adverse event will be obtained. Further, information from the patient tracking database and other records should be provided to justify the denominator for any adverse event rate calculations. The study should be designed to identify the major failure modes of the valve and establish their frequency, with particular attention to determining the likelihood and event rate of calcification. Complete results of the ongoing study should be reported in the annual reports. The results of the long-term study must be reflected in the labeling when the postapproval study is completed. The protocol should be submitted as a supplement for FDA review and approval within 45 days from the date of the PMA approval order.

3. To characterize valve performance as a function of chamber compliance and provide added assurance of safety in younger patients, complete hydrodynamic testing should be conducted to fully characterize the performance of the valve in 16 percent compliance chambers. This testing should be conducted according to the 1994 Heart Valve Guidance, or to an alternative protocol acceptable to FDA, that should be submitted within 45 days from the date of the PMA approval order.

FDA issued an approval order on November 24, 1997 The applicant's manufacturing facility was inspected and was found to be in compliance with the device Good Manufacturing Practice regulations

14. Approval Specifications.

Directions 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 and restrictions: See approval order.

The Approval Order, Summary of Safety and Effectiveness Data, and labeling can be found on the Internet at http://www.fda.gov/cdrh/pmapage.html.