

***Summary of Safety and Effectiveness Data
Omnicarbon™ Cardiac Valve Prosthesis***

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***Summary of Safety and Effectiveness Data
Omnicarbon™ Cardiac Valve Prosthesis***

1. GENERAL INFORMATION

Device Generic Name: Replacement Heart Valve

Device Trade Name: Omnicarbon™ Cardiac Valve Prosthesis

Models Available: Aortic Model 3313 and Mitral SupraAnnular Model 3523

Applicant's Name/Address: MedicalCV, Inc.
9725 South Robert Trail
Inver Grove Heights, Minnesota 55077
USA

Application Number: P830039/Supplement 7

Date of Notice of Approval to the Applicant: **JUL 26 2001**

2. INDICATIONS FOR USE

The Omnicarbon™ cardiac valve prosthesis is indicated for the replacement of dysfunctional native or prosthetic aortic or mitral heart valves.

3. DEVICE DESCRIPTION

The Omnicarbon™ cardiac valve prosthesis is an all pyrolytic carbon-coated mechanical-type valve prosthesis, with a single tilting disc (Figure 1). The valve design has three major components: the housing ring, disc, and suture ring.

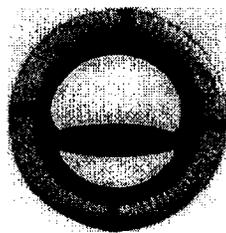


Figure 1
Omnicarbon™ Cardiac Valve Prosthesis

The disc is fabricated from pyrolytic carbon thickly coated over a graphite substrate containing tungsten (to allow radiographic visualization). The disc is slightly curved and retained within the housing ring by integral pivots and shields. The shields are small, fin-like structures projecting downstream from the housing ring, located 180° from each other on either side of the housing ring. The disc closes on the housing ring at a 12° angle relative to

the plane of the housing ring, and can open to a maximum angle of 80°. The disc rotates freely within the housing ring because there are no fixed hinges within the housing ring. Because there are no struts protruding across the flow orifice, the open disc separates the flow channel into two orifices.

The suture ring is constructed of polytetrafluoroethylene (PTFE). The seamless white fabric contains three (aortic) or four (mitral) black polyester markers to assist with suture placement during implantation. To allow optimal orientation of the prosthesis after implantation, the housing ring/disc assembly is rotatable within the suture ring.

The Omnicarbon™ cardiac valve prosthesis is available in the aortic and mitral configurations. The aortic valve, model 3313, is available in sizes 23, 25, 27, and 29 mm. The aortic valve suture ring has an intra-annular configuration. The mitral valve, model 3523, is available in sizes 27, 29, 31, and 33 mm. The mitral valve suture ring has a supra-annular configuration. Flow area dimensions of these valve sizes are listed in Figure 2. Sizes 27 and 29 mm share the same housing ring/disc assembly, with the suture ring compensating for the difference in tissue annulus diameter. Likewise, sizes 31 and 33 mm also employ identical housing ring/disc assemblies.

Figure 2
Omnicarbon™ Cardiac Valve Prosthesis Sizes



Size (corresponds to tissue annulus diameter, mm):	<u>23</u>	<u>25</u>	<u>27</u>	<u>29</u>	<u>31</u>	<u>33</u>
Disc Diameter, mm	18	20	22	22	24	24
Geometric Orifice Area, cm ²	2.5	3.1	3.8	3.8	4.5	4.5

4. CONTRAINDICATIONS

The Omnicarbon™ cardiac valve prosthesis is contraindicated in patients unable to tolerate anticoagulation therapy.

5. WARNINGS AND PRECAUTIONS

5.1 Warnings

For single use only. Do not resterilize.

If the Use-Before-Date on the package has expired, do not use the valve.

Carefully examine the labels and seals of the outer and inner packaging. If the accuracy or integrity of any of these labels or seals is in doubt, do not use this valve.

All accessory equipment must be disassembled after each use and thoroughly cleaned prior to resterilization. Routinely examine accessory equipment for damage or distortion prior to each use.

The outside of the rigid plastic exterior container (hardpack) is not sterile and must not be placed in the sterile field.

Dropped Valve: If you drop the valve, do not implant it.

Chipped or Scratched Valve Housing Ring or Disc: If the valve housing ring or disc is chipped or scratched, do not implant the valve.

Disengaged Disc: This may be caused by undetected handling damage or extreme pressure on the disc. Should disengagement occur, do not attempt to re-engage the disc into the valve housing; the valve should not be implanted.

Valves that have Come in Contact with Blood: Do not attempt to clean and resterilize such a valve for use in another person. Foreign protein transfer and/or residue from cleaning agents may cause a tissue reaction.

Catheterization: Passing a catheter, surgical instrument, or pacemaker lead through the Omnicarbon™ valve may cause serious valvular insufficiency, damage the valve, and/or cause catheter entrapment and, therefore, is not recommended.

5.2 Precautions

The innerpack and its contents are provided nonpyrogenic and sterile, and should be handled during surgical presentation with all necessary precautions to avoid contamination.

Oversizing occurs when too large a valve is forced into the tissue annulus. This may cause adjacent tissue to inhibit the free movement and full travel of the valve disc. If the obturator head does not pass easily through the tissue annulus, utilize the next lower size.

Use only OmniSeries/Omnicarbon accessories with the Omnicarbon™ valve.

Use only the OmniSeries™ collet or rotator to rotate the Omnicarbon™ valve. Under no circumstances should a surgical instrument be used to grasp the valve housing ring or disc. The valve disc should never be used as a lever to rotate the valve. Improper force or leverage on the disc may cause surface/structural damage or disc dislodgement.

If the Use-Before-Date on the package has expired, do not use the valve.

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Use only the OmniSeries™ collet or rotator to rotate the Omnicarbon™ valve. Under no circumstances should a surgical instrument be used to grasp the valve housing ring or disc. The valve disc should never be used as a lever to rotate the valve. Improper force or leverage on the disc may cause surface/structural damage or disc dislodgement.

7. MARKETING HISTORY

The Omnicarbon™ cardiac valve prosthesis has been marketed in Austria, Belgium, Brazil, Canada, Denmark, France, Germany, India, Italy, Japan, Netherlands, Peru, Russia, Spain, Sweden, and Switzerland.

There has never been a recall or a market withdrawal of the Omnicarbon™ cardiac valve prosthesis.

8. ADVERSE EVENTS

8.1 Potential Adverse Events

Adverse events potentially associated with the use of mechanical prosthetic cardiac valves include, but are not limited to (in alphabetical order):

angina	heart failure	stroke
cardiac arrhythmia	hemolysis or hemolytic anemia	structural dysfunction
clinically-significant	hemorrhage	thromboembolism
transvalvular regurgitation	myocardial infarction	tissue interference with
disc impingement/entrapment	nonstructural dysfunction	valve function
endocarditis or other infection	perivalvular leak	valve thrombosis

These events may lead to:

- permanent disability
- prosthesis explantation
- reoperation
- death

8.2 Observed Adverse Events

A multicenter, nonrandomized, prospective, international clinical study was conducted of patients implanted with an aortic and/or a mitral Omnicarbon™ cardiac valve prosthesis from August 27, 1984 through January 31, 1986. This study enrolled 354 patients at 5 institutions: 198 isolated aortic valve replacement (AVR), 115 isolated mitral valve replacement (MVR), and 41 aortic and mitral (double) valve replacement (DVR). Results of this initial clinical study were reported at 33 months, at which time the total cumulative follow-up was 555 patient-years.

Clinical results were updated at 4 of the initial study centers, creating a 14.6-year follow-up study. (The fifth center did not participate due to logistical reasons.) These long-term results included 232 patients (125 AVR, 70 MVR, 37 DVR), with a mean follow-up time of 9.9 ± 4.7 years (range 0.3 – 14.6 years) and 91% patient accountability. Total cumulative follow-up time of 2,152 patient-years was distributed as 1,198 AVR patient-years, 598 MVR patient-years, and 356 DVR patient-years. Adequate follow-up time was obtained for all three groups.

Table 1 shows the observed adverse events occurring during the early postoperative period.

Table 1: Early Postoperative Adverse Events

Event	n (% of cases)		
	AVR (125 pts.)	MVR (70 pts.)	DVR (37 pts.)
Death, all causes	4 (3.2)	6 (8.6)	2 (5.4)
Thromboembolism, All	5 (4.0)	0	0
Thromboembolism, TIA	2 (1.6)	0	0
Thromboembolism, Nontransient	3 (2.4)	0	0
Valve Thrombosis	0	1 (1.4)	0
Anticoagulant-Related Hemorrhage, major	0	1 (1.4)	0
Endocarditis	1 (0.8)	0	0
Perivalvular Leak, major	1 (0.8)	0	1 (2.7)
Pannus/Tissue Interference	0	0	0
Hemolytic Anemia	0	0	0
Structural Failure	0	0	0
Unacceptable Hemodynamics	0	0	0
Other Nonstructural Dysfunction	0	0	0
Reoperation	2 (1.6)	1 (1.4)	1 (2.7)
Explantation	2 (1.6)	1 (1.4)	0

Abbreviations: n = number of patients, pts. = patients
 AVR = aortic valve replacement, MVR = mitral valve replacement, DVR = double valve replacement
 TIA = transient ischemic attack

Table 2 lists linearized rates of late postoperative events for the patients-at-risk of each patient group. During the 14.6-year period, 69 patients died due to various causes. Valve replacement associated mortality was defined as death due to thromboembolism (7 cases), anticoagulant-related hemorrhage (5), sudden and unknown causes of death (8), endocarditis (3), perivalvular leak (3), and nonstructural dysfunction (1). The actuarial probabilities of freedom from adverse events at 5, 10, and 14 years are listed in Tables 3 and 4.

Table 2: Late Postoperative Events: Linearized Rates, %/patient-year ± SE (# of events)

	AVR	MVR	DVR
Patient-Years	1,198	598	356
Death, all causes	3.17±0.51 (38)	3.34±0.75 (20)	3.09±0.93 (11)
Death, valve-related/unexplained	1.34±0.33 (16)	0.67±0.33 (4)	1.97±0.74 (7)
Thromboembolism, All	0.92±0.28 (11)	0.33±0.24 (2)	0.56±0.40 (2)
Thromboembolism, TIA	0.25±0.14 (3)	0.33±0.24 (2)	0.28±0.28 (1)
Thromboembolism, Nontransient	0.67±0.24 (8)	0	0.28±0.28 (1)
Valve Thrombosis	0	0.17±0.17 (1)	0
Anticoagulant-Related Hemorrhage, major	0.67±0.24 (8)	0.50±0.29 (3)	0.56±0.40 (2)
Endocarditis	0.58±0.22 (7)	0	0.28±0.28 (1)
Perivalvular Leak, major	0.92±0.28 (11)	0.50±0.29 (3)	1.12±0.56 (4)
Pannus/Tissue Interference	0	0	0
Hemolytic Anemia	0	0	0
Structural Failure	0	0	0
Unacceptable Hemodynamics	0	0	0
Other Nonstructural Dysfunction	0.08±0.08 (1)	0.17±0.17 (1)	0
Reoperation	1.42±0.34 (17)	0.84±0.37 (5)	1.12±0.56 (4)
Explantation	1.09±0.30 (13)	0.67±0.33 (4)	0.28±0.28 (1)
Other: Minor Bleeding (no treatment)	0.58±0.22 (7)	0.67±0.33 (4)	0.84±0.49 (3)
Other: Perivalvular Regurgitation Without Hemodynamic Consequence (by echo)	0.42±0.19 (5)	0.17±0.17 (1)	0.84±0.49 (3)

Abbreviations: AVR = aortic valve replacement, MVR = mitral valve replacement, DVR = double valve replacement
 TIA = transient ischemic attack

Table 3
Late Postoperative Events: Actuarial Probability of Freedom from Event (life table method)
% ± SE at 5, 10, and 14 years Postoperative: Aortic Valve Replacement

Aortic Valve Replacement (AVR): cumulative follow-up = 1,198 patient-years			
Event	Freedom at 5 years	Freedom at 10 years	Freedom at 14 years
Death, all causes	82.8 ± 3.5	75.2 ± 4.1	63.7 ± 4.9
Thromboembolism, All	97.3 ± 1.5	92.6 ± 2.7	85.6 ± 4.3
Thromboembolism, TIA	99.1 ± 0.9	97.9 ± 1.5	95.6 ± 2.7
Thromboembolism, Nontransient	98.1 ± 1.3	94.5 ± 2.4	89.8 ± 3.6
Valve Thrombosis	100	100	100
Anticoagulant-Related Hemorrhage, major	96.4 ± 1.8	94.0 ± 2.4	92.7 ± 2.7
Endocarditis	94.1 ± 2.2	94.1 ± 2.2	94.1 ± 2.2
Perivalvular Leak, major	95.7 ± 1.9	94.6 ± 2.2	91.0 ± 3.3
Pannus/Tissue Interference	100	100	100
Hemolytic Anemia	100	100	100
Structural Failure	100	100	100
Unacceptable Hemodynamics	100	100	100
Other Nonstructural Dysfunction	99.1 ± 0.9	99.1 ± 0.9	99.1 ± 0.9
Reoperation	90.8 ± 2.7	89.7 ± 2.8	89.7 ± 2.8
Explantation	91.6 ± 2.6	90.5 ± 2.8	90.5 ± 2.8

Table 4
Late Postoperative Events: Actuarial Probability of Freedom from Event (life table method)
% ± SE at 5, 10, and 14 years Postoperative: Mitral Valve Replacement

Mitral Valve Replacement (MVR): cumulative follow-up = 598 patient-years			
Event	Freedom at 5 years	Freedom at 10 years	Freedom at 14 years
Death, all causes	89.7 ± 4.0	70.5 ± 6.2	62.4 ± 6.7
Thromboembolism, All	98.4 ± 1.6	98.4 ± 1.6	95.3 ± 3.5
Thromboembolism, TIA	98.4 ± 1.6	98.4 ± 1.6	95.3 ± 3.5
Thromboembolism, Nontransient	100	100	100
Valve Thrombosis	98.4 ± 1.6	98.4 ± 1.6	98.4 ± 1.6
Anticoagulant-Related Hemorrhage, major	96.8 ± 2.2	96.8 ± 2.2	93.8 ± 3.7
Endocarditis	100	100	100
Perivalvular Leak, major	100	93.0 ± 3.9	93.0 ± 3.9
Pannus/Tissue Interference	100	100	100
Hemolytic Anemia	100	100	100
Structural Failure	100	100	100
Unacceptable Hemodynamics	100	100	100
Other Nonstructural Dysfunction	100	97.6 ± 2.4	97.6 ± 2.4
Reoperation	98.4 ± 1.6	89.3 ± 4.6	89.3 ± 4.6
Explantation	98.4 ± 1.6	91.3 ± 4.2	91.3 ± 4.2

9. SUMMARY OF NONCLINICAL STUDIES

9.1 *In Vitro* Testing

The FDA's Draft Guidelines for Replacement Heart Valves (1982), ISO Standard 5840 for Cardiac Valve Prostheses, and subsequent particular data requests by FDA reviewers guided the *in vitro* studies performed for the Omnicarbon™ cardiac valve prosthesis. Although tested in the nonclinical studies, the clinical study (Section 10) did not generate sufficient data to support the safety and effectiveness of sizes 19, 21, 31, and 33 aortic valves and sizes 19-25 mitral valves.

9.1.1 Hydrodynamic Performance

Laser Doppler anemometry was used to visualize the flow pattern and flow velocities through the Omnicarbon™ valve design. Hydrodynamic studies were undertaken to characterize the effectiveness of the Omnicarbon™ valve to operate efficiently. Hydrodynamic testing of the valve demonstrated satisfactory forward and regurgitant flow. Tests were carried out under steady state and pulsatile flow conditions. Measurements included steady state pressure drops, pulsatile pressure drops, and regurgitant flow.

9.1.1.1 Steady Flow Experiments

Laboratory A

Steady flow tests were conducted in aortic and mitral test chambers in the applicant's laboratories, at flow rates of 5, 10, 15, 20, 25, and 30 liters/min. Three valves each of sizes 21 – 31/33 mm were tested. A Newtonian blood-analog fluid was used. Since the aortic and mitral valves have the same design, data differences were ascribed to the test chambers. Summary results are tabulated for three flow rates (Table 5) and are comparable to data obtained for a control valve (premarket approved by FDA) in all sizes.

Table 5
Steady State Pressure Drop

Valve Size (TAD)	Flow (L/min)	Mean ΔP (mmHg)
AORTIC		
21	5, 20, 30	0.5, 1.7, 2.8
23	5, 20, 30	0.4, 8.5, 18.1
25	5, 20, 30	0.2, 4.3, 9.4
27/29	5, 20, 30	0.1, 2.3, 5.0
31/33	5, 20, 30	0.1, 1.2, 2.9
MITRAL		
21	5, 20, 30	0.3, 1.8, 4.0
23	5, 20, 30	0.7, 11.6, 25.0
25	5, 20, 30	0.4, 8.0, 17.5
27/29	5, 20, 30	0.3, 5.6, 12.6
31/33	5, 20, 30	0.2, 3.8, 8.1

Note: The clinical study did not generate sufficient data to support the safety and effectiveness of sizes 19, 21, 31, and 33 aortic valves and sizes 19-25 mitral valves. The preclinical data for these sizes are included in the table (shaded values) since the results were used in the overall evaluation of the approved devices.

Laboratory B

A similar steady flow study was performed by an expert laboratory on sizes 19 – 33 mm, three samples each, in an aortic model at flow rates ranging approximately 50 – 1000 cm³/sec (3 – 60 L/min). The obtained pressure gradients were comparable to the above study at Laboratory A.

9.1.1.2 Pulsatile Flow Experiments: Pressure Drop

Laboratory A

Pulsatile flow pressure drop measurements were conducted in a calibrated pulse duplicator using a blood analog fluid. The same valves tested under steady flow conditions were tested under pulsatile conditions. Pressure drop was measured as a function of flow rate for each Omnicarbon™ valve size, three samples, at a pulse rate of 70 beats per minute (bpm). Data were collected at a minimum of 3 cardiac outputs, between approximately 3 and 8 L/min in most cases. Flow is expressed as the root mean square of the flow rate (Qrms). Each data point was established over 10 cycles, from which the mean and standard deviation were calculated. Table 6 provides a summary representative data at three flow rates. There was no discernible difference between the control valves (premarket approved) and Omnicarbon™ valves in either the mitral or aortic test chambers.

Table 6: Pulsatile Flow Summary (Laboratory A)
70 bpm, flow approximately 3 – 8 L/min

Omnicarbon Valve Size (TAD)	Aortic		Mitral	
	Qrms, L/min	ΔP, mmHg	Qrms, L/min	ΔP, mmHg
21	9.6	5.5	6.2	2.7
	13.9	7.5	9.6	5.7
	17.9	11.2	14.2	10.9
23	11.6	4.3	6.0	2.7
	17.9	10.5	9.5	4.8
	27.1	18.8	14.7	9.0
25	11.5	3.0	6.0	1.3
	17.6	5.2	9.5	3.3
	28.8	10.5	14.9	7.1
27/29	11.9	1.5	6.0	0.8
	19.4	3.1	10.0	2.3
	28.7	5.6	15.2	5.1
31/33	12.0	0.9	6.7	0.5
	17.9	2.8	10.2	1.5
	29.3	3.7	15.9	3.7

Note: The clinical study (Section 10) did not generate sufficient data to support the safety and effectiveness of sizes 19, 21, 31, and 33 aortic valves and sizes 19-25 mitral valves. The preclinical data for these sizes are included in the table (shaded values) since the results were used in the overall evaluation of the approved devices.

Table 6: Pulsatile Flow Summary (Laboratory A)
70 bpm, flow approximately 3 – 8 L/min (continued)

Control Valve Size (TAD)	Aortic		Mitral	
	Qrms, L/min	ΔP , mmHg	Qrms, L/min	ΔP , mmHg
21	9.4	4.7	6.2	2.9
	13.6	9.2	9.7	6.9
	18.0	13.8	14.7	11.9
23	11.8	5.1	6.4	2.3
	18.5	10.6	9.6	4.7
	27.1	18.6	14.7	9.0
25	12.2	3.3	6.2	1.3
	18.5	5.8	9.5	3.5
	29.0	11.4	15.2	6.3
27/29	12.3	1.6	6.2	1.2
	19.2	3.2	10.3	3.0
	28.8	7.4	15.3	5.7
31/33	12.1	1.0	6.6	0.7
	18.7	2.0	10.4	1.4
	29.3	3.5	15.9	3.6

Note: The clinical study (Section 10) did not generate sufficient data to support the safety and effectiveness of sizes 19, 21, 31, and 33 aortic valves and sizes 19-25 mitral valves. The preclinical data for these sizes are included in the table (shaded values) since the results were used in the overall evaluation of the approved devices.

The effect of variation in heart rate was examined for four sizes at 50, 70, and 100 bpm and 5 L/min flow rate. Three samples of four representative valve sizes (19, 23, 25, and 31/33) were tested. Measurements suggest a slight increase (up to 2 mmHg) in the mean pressure drop with increased flow rate. The larger differences are observed in the smaller sizes.

Laboratory B

Pulsatile flow experiments (Table 7) were conducted under similar laboratory conditions as those in Laboratory A. Two samples each of sizes 21 – 27/29 mm were tested in the aortic chamber, and the mitral chamber was used for sizes 23 – 31/33 mm, at 70 bpm. Flow (Qrms) ranged from 9 to 24 L/min. A control valve (premarket approved) was used for every size and found to be comparable to the Omnicarbon™ valve data. Laboratories A and B reported comparable results.

Table 7
In Vitro Pulsatile Flow, Laboratory B

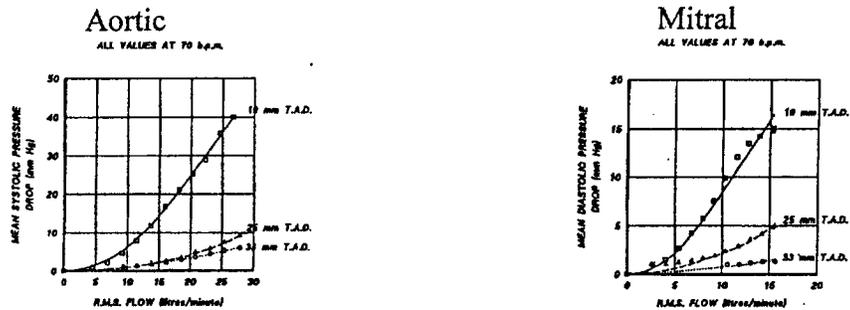
Omnicarbon Valve Size (TAD)	Aortic		Mitral	
	Flow Qrms, (L/min)	Pressure Differential $\overline{\Delta P_s}$ (mmHg)	Flow Qrms, (L/min)	Pressure Differential $\overline{\Delta P_d}$ (mmHg)
21	18.0	10.6		
	15.0	7.7		
	12.0	5.2		
	10.0	3.8		
23	24.0	9.5	13.0	6.6
	20.0	7.1	11.0	4.5
	15.0	3.8	9.0	3.2
	12.0	2.4	7.0	2.0
25	24.0	5.7	14.0	2.8
	20.0	4.0	11.0	2.1
	15.0	2.4	9.0	1.9
	12.0	1.6	7.0	1.4
27/29	24.0	3.0	15.0	3.5
	20.0	2.2	13.0	2.7
	15.0	1.4	11.0	1.7
	12.0	0.8	9.0	1.2
31/33			15.0	1.8
			13.0	1.3
			11.0	0.9
			9.0	0.6
Control Valve Size (TAD)	Flow Qrms, (L/min)	Pressure Differential $\overline{\Delta P_s}$ (mmHg)	Flow Qrms, (L/min)	Pressure Differential $\overline{\Delta P_d}$ (mmHg)
21	18.8	1.9		
	13.1	5.8		
	11.2	3.91		
23	24.9	10.4	11.8	5.46
	19.3	6.35	9.2	3.5
	12.0	2.57	7.0	1.96
25	26.5	6.15	14.8	5.16
	19.0	3.62	11.5	3.25
	12.5	1.59	8.9	1.97
27/29	25.6	3.09	15.3	3.41
	19.8	1.84	11.8	2.15
	13.0	1.05	9.1	1.29
31/33			16.8	1.82
			12.1	1.09
			9.5	0.75

Note: The clinical study (Section 10) did not generate sufficient data to support the safety and effectiveness of sizes 19, 21, 31, and 33 aortic valves and sizes 19-25 mitral valves. The preclinical data for these sizes are included in the table (shaded values) since the results were used in the overall evaluation of the approved devices.

Laboratory C

This study was conducted according to the British and International Standards testing guidelines (BS 6444:1990, ISO 5840: 1989 "Cardiovascular implants: Part 1: Methods of test for heart valve substitutes and requirements for their packaging and labeling"). The pulsatile flow pressure drop of 3 Omnicarbon™ valve sizes (19, 25, and 31/33 mm, one sample each) was examined using saline solution at room temperature. Four cardiac outputs were simulated between the range of 2 L/min and 8 L/min, and 10 measurements were made of each parameter. Heart rate varied from 40 bpm to 140 bpm. Additional experiments of cardiac output ranging from 1.4 L/min to 8.4 L/min at a fixed heart rate of 70 bpm were performed. The results obtained are shown in Figure 3 and seem comparable to data reported by Laboratories A and B. (Note: The clinical study (Section 10) did not generate sufficient data to support the safety and effectiveness of sizes 19, 21, 31, and 33 aortic valves and sizes 19-25 mitral valves.)

Figure 3
Mean Pressure Drop, mmHg vs. Qrms Flow, L/min



9.1.1.3 Regurgitation

Laboratory A

Closing and leakage regurgitation were measured in sizes 19, 23, 25, and 31/33 mm valves (3 samples each) in aortic and mitral test channels. Valves were tested at 5 L/min with beats per minute varying among 50, 70, and 100 in a 37° C blood analog solution. Table 8 lists regurgitation data produced from these test conditions, as percent of cardiac output. Controls (premarket-approved) were employed for every size, and the results are comparable to the test valve.

Table 8
Regurgitation (%) at 5 L/min

Beats per Minute	Omnicarbon Valve Size (TAD)	Aortic			Mitral		
		% Closing	% Leakage	% Total Regurgitation	% Closing	% Leakage	% Total Regurgitation
50	19	1.6	2.1	3.7	1.3	1.2	2.5
	23	2.0	2.1	4.0	2.1	1.2	3.3
	25	2.9	2.1	5.0	2.9	1.1	4.0
	31/33				7.3	1.2	8.5
70	19	1.9	2.1	4.0	1.9	1.2	3.1
	23	2.3	2.1	4.4	2.9	1.2	4.1
	25	3.9	2.0	5.9	4.2	1.1	5.2
	31/33				9.5	1.2	10.7
100	19		2.0	5.4	2.8	1.1	3.9
	23	3.9	2.0	5.8	4.1	1.1	5.2
	25	5.5	2.0	7.5	7.7	1.0	8.7
	31/33				12.8	1.0	13.8
Beats per Minute	Control Valve Size (TAD)	% Closing	% Leakage	% Total Regurgitation	% Closing	% Leakage	% Total Regurgitation
50	19	1.2	2.8	4.0	1.6	1.6	3.2
	23	2.7	3.0	5.7	2.4	1.7	4.0
	25	2.7	3.1	5.8	2.8	1.8	4.7
	31/33			9.2	7.3	2.1	9.4
70	19	1.9	2.8	4.7	2.5	1.6	4.1
	23	3.4	2.9	6.3	3.4	1.6	5.0
	25	4.0	3.2	7.3	4.0	1.7	5.7
	31/33				9.8	2.0	11.9
100	19	2.2	3.0	5.2	3.5	1.6	5.1
	23	5.0	2.7	7.6	4.7	1.6	6.2
	25	5.0	3.2	8.2	6.9	1.7	8.5
	31/33				13.6	1.8	15.4

Note: The clinical study (Section 10) did not generate sufficient data to support the safety and effectiveness of sizes 19, 21, 31, and 33 aortic valves and sizes 19-25 mitral valves. The preclinical data for these sizes are included in the table (shaded values) since the results were used in the overall evaluation of the approved devices.

Worst case analysis of regurgitation volume, to mimic a failing heart, was determined for three sizes, 23, 25, 31/33 (3 samples each), at low flow (3 L/min) and high frequency (100 bpm), in both the aortic and the mitral test systems. The same control valve model was used as for determination of regurgitation at standard (5 L/min) flow. As expected, in both aortic and mitral positions higher regurgitation (19% – 28%) was observed, particularly for larger sizes for both the test valves and controls at this low flow with high frequency. Results for test valves and controls were comparable.

Laboratory B

The regurgitation performance of the Omnicarbon™ and control valves was examined using equipment similar to that used in Laboratory A. Two samples of each valve size were used, and averaged results were comparable to the data measured for the control valves (Table 9). Control valve data for 70 bpm were given in tabular form, data for the other frequencies were provided only in graphical form.

Table 9
Total Regurgitation: % of Cardiac Output at 5 L/min

Valve Position	Valve Size, TAD	Frequency, bpm			
		Omnicarbon 50	Omnicarbon 70	Control 70	Omnicarbon 100
Aortic	21	6.4	7.8	7.9	8.8
	23	8.1	9.5	9.8	10.8
	25	9.0	10.1	10.3	10.9
	27/29	10.2	11.2	11.4	12.2
Mitral	23	8.9	10.0	10.3	11.2
	25	9.9	11.0	11.4	12.0
	27/29	10.8	11.8	12.0 - 13.5	13.0
	31/33	13.0	14.2	14.2 - 15.1	14.9

Note: The clinical study (Section 10) did not generate sufficient data to support the safety and effectiveness of sizes 19, 21, 31, and 33 aortic valves and sizes 19-25 mitral valves. The preclinical data for these sizes are included in the table (shaded values) since the results were used in the overall evaluation of the approved devices.

Laboratory C

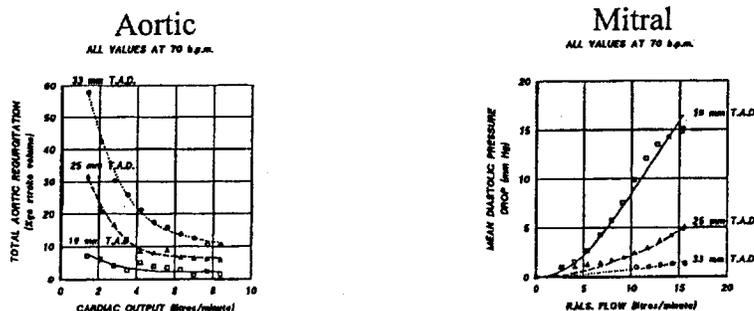
Three samples of all sizes (19 – 31/33 mm) were examined to measure leakage (using steady flow) and closing volume (pulsatile flow). Conditions to measure the closing volume ranged from stroke volume of 30 – 75 mL and frequency of 42 bpm to 150 bpm (corresponding to cardiac output of 1.5 – 8 L/min). Leakage volume was determined from standard curves of steady backflow measurements through the closed valve and under various pressure differences. The average regurgitation volume (closing + leakage volumes) for all pumping conditions were found to range 1.6 – 5.3 mL for sizes 19 – 31/33 mm. Note: The clinical study (Section 10) did not generate sufficient data to support the safety and effectiveness of sizes 19, 21, 31, and 33 aortic valves and sizes 19-25 mitral valves.

Laboratory D

Valve regurgitation was determined from one sample each of three sizes 19, 25, 31/33. Cardiac output varied from 2 to 8 L/min, in both aortic and mitral testing channels, and the frequency was maintained at 70 bpm. Figure 4 shows curves derived from the data generated by these experiments. This laboratory reported that findings for the Omnicarbon™ valve indicate comparable valve performance to various size 25 tilting-disc valve controls

models, however, the laboratory did not identify the control valves nor did it provide individual data for each control valve. Note: The clinical study (Section 10) did not generate sufficient data to support the safety and effectiveness of sizes 19, 21, 31, and 33 aortic valves and sizes 19-25 mitral valves.

Figure 4
Total Regurgitation (with varying cardiac output)



Laboratory E

Another expert independent laboratory published a study including the Omnicarbon valve and five other mechanical valves with premarket approval (size 27) in an aortic model that reported energy losses from the three phases of the cardiac valve cycle: opening, closing, and leakage at 4 flow rates (3.0, 4.5, 6.5, 8.0 L/min). Cardiac energy losses during the open phase ranged ~1.5% to ~7.0% among these six valve models, while regurgitation ranged ~1.5% to ~9.4%. Total energy loss in these six valve models ranged from ~5.7% to ~12.0% of cardiac energy. The Omnicarbon™ valve exhibited approximately 3% loss of cardiac energy during the opening (forward flow) phase, and a total energy loss of approximately 5.7% at 4.5 L/min. This study found the Omnicarbon™ valve performance comparable to the other five premarket-approved valve models, however leakage energy loss and overall energy loss were reported to be lowest for the Omnicarbon™ valve.

9.1.1.4 Flow Visualization and Laser Doppler Anemometry

Pulsatile flow laser Doppler anemometry was used to visualize the flow pattern and velocities through the size 27 aortic and mitral valves. These tests were performed using a beat rate of 70 bpm and a cardiac output of 6 L/min. Velocity profiles were obtained at peak systole and diastole. Mean shear stresses ranged from 60 – 600 dynes/cm². Data for the control valve were not provided.

9.1.1.5 *In Vitro* Ultrasound

Doppler estimation of pressure drop as a function of flow rate was conducted on aortic sizes 19, 21, and 29 mm (3 samples each), and 25 mm (1 sample), and mitral sizes 23, 31 mm (3 samples each), 27 mm, and 31 mm (1 sample each), with no other model used for comparison. Peak and mean pressure drop were calculated at four flow rates. Analysis of the curve showed good linear fit of the curve for pressure drop versus flow rate. Note: The clinical study (Section 10) did not generate sufficient data to support the safety and effectiveness of sizes 19, 21, 31, and 33 aortic valves and sizes 19-25 mitral valves.

9.1.2 Structural Performance

Safety tests were performed on the Omnicarbon™ valve (models 3313/3523) to determine failure forces of various components (including the suture ring) and for integrity of the disc/housing mechanism. Failure forces were compared with physiological forces to deduce safety factors. These safety factors were judged to be satisfactory.

9.1.2.1 Material Characterization

Both the housing ring and the disc are manufactured as a composite, a graphite substrate coated with Pyrolite® by Sulzer CarboMedics, Inc. (Texas) according to MedicalCV, Inc. specifications. The applicant provided detailed material properties for Pyrolite. In addition, fracture mechanics studies revealed a fracture toughness value of approximately 1 MPa√m and fatigue crack growth rate of $da/dN = 4.15 \times 10^3 (\Delta K)^{88.9}$ in units of m/cycle. Static stress corrosion crack testing measured a worst case crack growth rate of $da/dt = 1.36 \times 10^{-7} (\Delta K)^{13.8}$ m/sec.

9.1.2.2 Finite Element Analysis

Two independent laboratories performed three-dimensional finite element analyses to determine the location and intensity of stresses in the valve's housing ring and disc, in both the closed and fully-open positions (Table 10).

Table 10
Stress Analysis

Laboratory	Valve Size, TAD	Method	Results
A (year 1986)	31/33	Static loading, disc closed, uniform pressure 300 mmHg, Modified Mohr Theory	Max. nodal Stress (MPa): disc 32.7; housing 57.3 Max. element stress: disc 20.6; housing 104.2 Safety factor: disc 14.8; housing ring 12.6
		Static loading, disc fully open, peak flow 50 L/min, Modified Mohr Theory	Max. nodal Stress (MPa): disc 8.8; housing 53.1 Max. element stress: disc 7.2; housing 22.3 Safety factor: disc 18.2; housing ring 12.9
B (year 1995)	All sizes, (19, 21, 23, 25, 27/29, 31/33)	Static loading, disc closed (various positions), Pressure 200 mmHg, in-tolerance coating thickness, residual stress included, Algor software.	Max. stress in disc (psi): symmetric 1169–2284; asymmetric, 1283–2771 Max. stress in pivots (psi): symmetric top, 769–1006; symmetric bottom, 407–769; asymmetric top, 989–1145; asymmetric bottom 461–639 For minimal-coated components (psi): discs: symmetric, 1423–2853, asymmetric, 1562–3461; pivots: top 988–1294, bottom 527-997

Note: The clinical study (Section 10) did not generate sufficient data to support the safety and effectiveness of sizes 19, 21, 31, and 33 aortic valves and sizes 19-25 mitral valves.

9.1.2.3 Transient Stresses During Closure

Publications and testing on monoleaflet valves have outlined a detailed pressure distribution across the valve at the moment of closure. It is estimated that at the instant of closure there is a pressure gradient across the valve

inducing backflow in addition to the pressure transients induced by the sudden stopping of the occluder by the housing. The pressure distribution on the under side of the occluder is estimated to be a minimum of -743 mmHg at the major orifice tip tapering to zero at the pivot axis and rising to 381 mmHg at the minor orifice tip. The pressure distribution on the top of the orifice is estimated as a combination of a constant pressure and the tapered distribution. At the major orifice end it is 773 mmHg: the pressure tapers to zero at the pivot axis and then falls to -352 mmHg at the minor orifice tip. The finite element analysis using this load case determined a maximum tensile stress on the occluder of 1640 psi, which is less than the 2284 psi predicted for the 200 mmHg static loading case. Overall the valve is able to withstand this type of loading because of the large amount of seat area. Because the greatest pressure occurs adjacent to the major orifice seat, most of the load is transferred directly to the seat and does not create the bending stresses seen with the static load case.

9.1.2.4 Assembly Stresses

Omnicarbon™ valves are assembled using size-specific fixtures in order to minimize the assembly stresses. Finite element analyses of models of worst-case tolerance valve components of all sizes were performed to estimate the assembly stresses on each component. It was determined that the highest assembly stresses occur on parts with maximum coating thickness. This worst-case analysis concludes that the assembly stresses in both the coating and substrate yield a reasonable margin of safety. For example, the worst case component estimates a maximum assembly stress of 39 Ksi which can be compared to the nominal tensile strength of 51 Ksi for the pyrolytic carbon coating.

9.1.2.5 Residual Stress

The strain gage and sectioning technique measures residual stress near the surface of a material. The method involves mounting a strain gage on the surface of a component, sectioning off the gage part, removing the substrate, and measuring the strain induced. The measured strains are then related to the residual principal stresses by fundamental equations.

Residual stress determination was conducted on a total of eight discs and eight housing rings. The values of the principal and maximum residual stresses were determined, for both discs and housing rings, as close as possible to the area of maximum service stress. Uniaxial strains were measured from rosette gages and principal stresses were calculated from the residual strain data. The consistency of the maximum residual stress within a particular size component was determined with three discs for valve size 25 mm (disc diameter 20 mm) and three size 31/33 mm housing rings (disc diameter 24 mm). The magnitude of the maximum residual stress on the components ranges from 2 to 5 Ksi for discs, and from 1 to 5 Ksi for housing rings. The principal

residual stresses are tensile on the discs and both tensile and compressive on the housing rings.

9.1.2.6 Fatigue/Crack Propagation and Valve Lifetime

Damage tolerance analysis was performed to determine if inherent flaws present due to the manufacturing process will grow to failure.

Fracture mechanics tests were performed in order to measure the fracture toughness and subcritical crack growth rates due to cyclic loading and stress corrosion cracking in Pyrolite® carbon. Tests were performed in air and in Ringer's solution, and the material was found to exhibit resistance curve behavior with a fracture toughness (K_{Ic}) of approximately $1 \text{ MPa}\sqrt{\text{m}}$. Fatigue and static stress corrosion crack growth rates were measured at stress intensity ranges, ΔK , between 0.5 and $1.5 \text{ MPa}\sqrt{\text{m}}$. Fatigue tests were run with a load ratio (R) of 0.1 at a frequency of 50 Hz . Using Paris law coefficients, worst case crack growth rate was determined to be $da/dt = 1.36 \times 10^{-7} (\Delta K)^{13.8} \text{ m/sec}$ for stress corrosion.

The finite element analysis performed for each size Omnicarbon™ valve was described under 9.1.2.2. Maximum stresses on valve components occur when the valve is closed and a pressure gradient exists across the valve disc. The effect of disc position relative to the valve housing and of coating thickness variations on the stress level in the components were also considered.

The results of the finite element stress analysis along with the report on residual stress levels in the valve components and the fracture toughness results were analyzed to calculate the critical crack size that will result in valve failure and the initial crack size that will not grow to the critical crack size in 100 years of service. Initial cracks that will not grow to critical size in 100 years are given in Table 11.

Table 11
Initial Crack Size

Location	μm
Pivot Edge	< 65
Housing Surface	< 216
Disc Edge	< 85.9
Disc Surface	< 281

It should be noted that the disc crack growth calculations assume that the disc is cycled continuously at 200 mmHg and that the flaw is continuously at the high stress point. The disc freely rotates in the housing ring, which makes it unlikely that the same spot on the disc would continuously encounter the high stress levels used for the crack propagation analysis.

9.1.2.7 Proof Pressure Test

Based on the previously-described fatigue and crack propagation analyses, proof stress—the stress level that must be induced into the high tensile stress regions in order to cause component fracture if the component contains a crack larger than those listed in Table 11—was estimated for all valve sizes. These stress levels were used in the development of a proof test that would eliminate any pre-existing cracks that might lead to fatigue failure in less than 100 years *in vivo*. All valves are subjected to this proof test that exposes the assembly to a high pressure specific to each size. Assemblies containing cracks larger than those shown in Table 11 are expected to fail during the proof test and be scrapped.

9.1.2.8 Static Failure Experiments

Static load to failure tests were performed on the largest-size (housing ring 31/33 mm TAD, 24 mm disc diameter) valve components (inflow pivots, shields, disc, and housing ring). Physiological loads were calculated to determine safety factors (Table 12).

Table 12: Static Load to Failure

Support Member	Physiological Load (N)	Static Load to Failure (N)	Safety Factor
Inflow Pivot	4.8	167	35
Shield	0.8	137	171
Disc (open)	0.8	89	111
Housing Ring	18.4	362	19.7

9.1.2.9 Suture Ring Dislodgement

Suture ring dislodgement force was tested for the three largest Omnicarbon™ mitral valve sizes: 29, 31, and 33 mm TAD. Ten samples of each size were evaluated in a custom fixture using a universal test machine. The dislodgement force of all test samples exceeded 35 lbs. (test limit), which indicated a high degree of safety. Similarly, the Omnicarbon™ aortic valve was tested, sizes 19, 21, 23, 25, and 33 mm (3 samples each), and all samples showed similar results. Note: The clinical study (Section 10) did not generate sufficient data to support the safety and effectiveness of sizes 19, 21, 31, and 33 aortic valves and sizes 19-25 mitral valves.

9.1.2.10 Disc Sticking/Housing Ring Deformation

Measurement of the radial force necessary to deform the housing ring (without suture ring) to the point where it inhibits disc movement (sticking) was performed for each valve size (19, 21, 23, 25, 27/29, and 31/33 mm). Three samples were tested for each size. Two size 27 mm control valves (both with premarket approval), one with a metal housing ring and the other with a pyrolytic carbon housing ring, were also tested. Deformability forces were highest with the metal housing ring and lowest in the pyrolytic carbon control

valve. The Omnicarbon™ valve measurements ranged from approximately 45 to 175 N. As expected, smaller valves required higher deformation forces. Note: The clinical study (Section 10) did not generate sufficient data to support the safety and effectiveness of sizes 19, 21, 31, and 33 aortic valves and sizes 19-25 mitral valves.

9.1.2.11 Disc Dislodgement

Experiments on all valve sizes (minimum 6 samples each) recorded the force required to dislodge the disc in the fully-open position. Using the minimum curve fit of the data, minimum dislodgement force was calculated for each size. These non-dimensional force terms were used to calculate the actual dislodgement force. Using this conservative approach (minimum curve fit), the minimum dislodgement force is at least 13 N, resulting in a minimum safety factor of 22 (Table 13).

Table 13: Minimum Dislodgement Force and Safety Factors

Valve Size (TAD)	Minimum Dislodgement Force (N)	Physiological Load (N)	Safety Factor
21	14.1	.258	54.5
23	16.9	.330	51.3
25	14.5	.407	35.6
27/29	13.9	.492	28.3
31/33	13.2	.586	22.4

Note: The clinical study (Section 10) did not generate sufficient data to support the safety and effectiveness of sizes 19, 21, 31, and 33 aortic valves and sizes 19-25 mitral valves. The preclinical data for these sizes are included in the table (shaded values) since the results were used in the overall evaluation of the approved devices.

9.1.2.12 Cyclic Failure—Fluid Loading

Six largest-size (disc diameter 24 mm) Omnicarbon™ valves were studied for low-cycle (<10⁶ cycles) failure in a high pressure pulse duplicator apparatus. Peak pressure drops occurred when the disc was closed.

Three groups, consisting of 2 valves each, were subjected to cyclic pressures of 40, 50, and 60 psi (0.28, 0.34, and 0.41 MPa). One valve failed at 60 psi (0.41 MPa) after approximately 235,000 cycles. All other units sustained test pressures with no failures beyond 10⁶ cycles.

9.1.2.13 Accelerated Wear

Two accelerated wear experiments were performed, one using size 27/29 mm TAD (disc diameter 22 mm) and the other using size 31/33 mm TAD (disc diameter 24 mm). In both experiments, 14 Omnicarbon™ valves were evaluated: two at 1, 2, 3, and 6 equivalent years, and the remaining six at 10 equivalent years. In both experiments, the depth (d) and width (w) of the wear track were measured on both housing ring shields. The maximum depth of

wear was measured on the inflow and outflow sides of the disc, and on the edge of the disc.

One experiment used 14 Omnicarbon™ valves, and 2 of another valve model (premarket-approved) of the same size were included for control and comparison. During this test, reverse osmosis water was used as the testing fluid. The second accelerated wear experiment employed another monoleaflet valve design as a control, reverse osmosis water was replaced with blood analog (glycerol/water solution), and 14 of the largest-size Omnicarbon™ valves were studied. The wear observed in this experiment was exceptionally low. Refer to Table 14 for the 10-year wear summary. The shield and disc wear data were fitted to a linear regression, and both test and control valves exhibited similar wear.

Table 14
Accelerated Wear: 10-Year Equivalent, *In Vitro* (µm)

Location of Wear	Experiment No. 1: Test Fluid Water	Experiment No. 2: Test Fluid Blood Analog
Inflow or Outflow Surface	0.20–0.82	0.14–0.28
Disc Edge	0.82–1.4	0.14–0.41
Shields	0.82–2.46	0.14–0.28

Wear and Dislodgement

The dislodgement force ultimately will be affected by the amount of wear of both the shield and disc. Given enough time, wear will allow the disc to escape. The length of time can be predicted using the rate of wear for the shields and disc as determined from the wear experiment. This analysis predicts that it will take longer than 560 years before wear reduces the dislodgement force to two times the physiological force, based on the worst-case water test fluid data. Also, this analysis indicates that the wear rate is small enough that the dislodgement force is not significantly affected by wear through the life expectancy of the valve.

In addition, dislodgement tests were done on six 10-year Omnicarbon™ accelerated wear test samples and four Omnicarbon™ control (uncycled) samples to verify their safety and the dislodgement force analysis. Consistent with that analysis, these results do not indicate any significant change in dislodgement force after ten years of wear.

Based on the blood analog wear data, over 7,700 years are needed for the Omnicarbon™ disc to dislodge due to "physiological forces" (0.8N), and nearly 9,000 years are required for wear to reduce the Omnicarbon™ valve coating thickness to the point of exposing its substrate. The lower wear observed in the blood analog medium is probably due to the lubricant effect of glycerol.

9.1.2.14 Cavitation Testing

Testing of the potential for cavitation in the Omnicarbon™ valve design was performed in accordance with the October, 1994 *Draft Guidance for Replacement Heart Valves*.

Three Omnicarbon™ size 33 mm valves (disc diameter 24 mm) and two other size 33 mm premarket-approved valve models (controls) were tested with their suture rings (elastic mounting), and then again with the suture rings removed (rigid mounting). In the compliant system, none of the valves exhibited signs of cavitation when tested to $dp < 5000$ mmHg/second. The rigid system, however, generated cavitation. Location of the observed cavitation bubbles was confined to a small area at the contact line of the disc and the housing ring, at the side opposite the tilting axis. Cavitation thresholds for all three different valve models are in the same general range of values (3200 – 3660 mmHg/sec); the Omnicarbon™ valve average of 3 measurements (3660 mmHg/sec) was the highest threshold value.

9.2 Animal Testing

The Omnicarbon™ valve animal implant program was designed to evaluate the following parameters: hemodynamic performance, *in vivo* thrombogenicity, cineangiography, and hemolytic effects of the valve.

Five canines completed the three-month study period without complications and underwent blood evaluation approximately every two weeks postoperatively. At the end of the three-month postoperative period, all blood values were within normal ranges.

All five animals underwent right and left heart catheterization just prior to being sacrificed and autopsied. Generally, angiography verified normal cardiac outputs, minimal valve regurgitation, minimal valve gradients, and an adequate range of disc motion for each of the valves.

All five animals underwent autopsy immediately after being sacrificed. The Omnicarbon™ valves had been implanted for 93 – 103 days. The heart and lungs were examined for any gross pathology. Histological sections were obtained from the heart, lungs, brain, liver, kidneys, and spleen. The major organs and brain were all closely examined for any abnormal pathology. There was no evidence of thrombus on any valve and all the valves appeared to have complete mechanical function. The pathology of all the major organs was unremarkable and all the animals appeared to have been relatively healthy.

In conclusion, this animal implant study demonstrated no significant problems in suturing or handling the Omnicarbon™ valve, and postoperative catheterization results confirmed that the valve has minimal gradient and minimal regurgitation. Hematology studies showed an improving trend as implant time progressed, with all values within normal ranges at the end of the study.

9.3 Sterilization and Shelf Life

The Omnicarbon™ cardiac valve prosthesis is provided sterile, in a double microbial barrier package system. A terminal ethylene oxide process sterilizes the product to a sterility assurance level of at least 10^{-6} by a cycle validated using decimal reduction and half-time cycle studies. Ethylene oxide residuals at the time of product release are demonstrated to be within acceptable limits according to the ISO and FDA recommendations (ANSI/AAMI/ISO 10993-7 and Federal Register 43:27474-27483, 1978; 64:37546-37551, 1999).

Real-time aging studies of the OmniSeries™ package system demonstrate that the package is not damaged by the anticipated conditions of handling or shipping. Furthermore, the package retains its sterile barrier properties for at least 10 years after sterilization.

The Omnicarbon™ valve should not be resterilized by a clinical facility.

Implantation accessories are reusable and must be cleaned and sterilized by the clinical facility. Sterilization of accessory components may be achieved using steam or ethylene oxide terminal sterilization processes. MedicalCV, Inc. validated the efficacy of the recommended sterilization cycles. Conventional steam sterilization (30 minutes at 121°C/250°F), flash steam sterilization (10 minutes at 132°C/270°F), and ethylene oxide gas exposure (725 mg/L, 70% RH, 55°C/131°F, 60 minutes) each demonstrated effective sterilization of the accessory pieces.

10. SUMMARY OF CLINICAL STUDIES

Complications observed during the clinical studies—safety endpoints—are provided in Section 8.2 of this document. Hematology data also provide safety information. These figures give confidence that the Omnicarbon™ valve design has no worsening trends, i.e., long-term deleterious effects on blood cells. Blood studies performed approximately 13½ years postoperatively are summarized in Table 15. No clinically-significant hemolysis (hemolytic anemia) was detected. The clinical study did not generate sufficient data to support the safety and effectiveness of sizes 19, 21, 31, and 33 aortic valves and sizes 19 – 25 mitral valves.

Table 15
Late Postoperative Blood Values by Implant Position

Parameter	AVR mean±SD (n)	MVR mean±SD (n)	DVR mean±SD (n)
Hemoglobin, males, <i>g/dL</i>	14.8±1.4 (46)	14.2±2.2 (13)	14.2±1.9 (8)
Hemoglobin, females, <i>g/dL</i>	13.6±1.0 (11)	14.1±1.2 (15)	13.2±1.7 (7)
Hematocrit, males, %	44±4 (43)	42±6 (13)	42±5 (8)
Hematocrit, females, %	40±2 (11)	41±3 (15)	39±5 (7)
Red Blood Cells, males, $10^6/\mu\text{L}$	4.86±0.61 (45)	4.77±0.65 (13)	4.50±0.63 (8)
Red Blood Cells, females, $10^6/\mu\text{L}$	4.42±0.27 (11)	4.54±0.38 (15)	4.29±0.65 (7)
Reticulocytes % <i>RBC</i>	1.3±0.6 (46)	1.1±0.5 (25)	2.2±1.6 (13)
White Blood Cells $10^3/\mu\text{L}$	7.0±1.8 (53)	6.7±1.7 (28)	6.5±1.7 (15)
Lactate Dehydrogenase % <i>upper normal</i>	97±28 (46)	109±38 (32)	142±61 (11)
Haptoglobin % <i>lower normal</i>	48±71 (44)	83±120 (24)	29±34 (15)

Effectiveness endpoints of the clinical studies were the New York Heart Association (NYHA) functional classification and echocardiographic assessments. Patient demographic information is presented in Tables 16 (preoperative) and 17 (operative), followed by the effectiveness results in Tables 18 – 20. These tables present data pertaining to the patient cohort studied in the 14.6-year follow-up. Section 8.2 gives more information regarding the initial and the long-term clinical follow-up studies, including the accumulated patient time of Omnicarbon™ valve experience.

Table 16
Population Demographics

Patients	232 (125 AVR, 70 MVR, 37 DVR)
Gender	167 males, 65 females
Age at Implantation	49 ± 12 years (range 14 – 71) AVR: 49 ± 13, MVR: 50 ± 11, DVR: 49 ± 11
Disease Etiology (some patients experienced multiple conditions):	
	Rheumatic 54%
	Endocarditis 10%
	Prosthetic Valve Dysfunction 9%
	Congenital 9%
	Myxomatous/Mucinous 4%
	Marfan Syndrome 3%
	Cystic Medial Necrosis 1%
	Other (e.g., calcification, trauma) 13%
	Undetermined 4%
Preoperative NYHA Classification	2% Class I 26% Class II 57% Class III 14% Class IV 1% Undetermined

Table 17
Operative Information

Previous Cardiac Surgical Procedures:		<u>number of patients</u>
	Coronary Artery Bypass Graft	2
	Previous Prosthetic Valve	20
	Aortic Graft	1
	Commissurotomy	11
Concomitant Cardiac Surgical Procedures:		
	Coronary Artery Bypass Graft	15
	Aortic Graft	12
	Aortic Root Reconstruction	4
	Aneurysm Repair	1
	Annuloplasty	12
	Commissurotomy	3
	Permanent Pacemaker	2
	Miscellaneous (e.g., ASD/VSD repair)	15
Implant Distribution	AVR 54%, MVR 30%, DVR 16%	
Valve Size (includes DVR)	<u>Aortic (# of patients)</u>	<u>Mitral (# of patients)</u>
21 mm	7	0
23 mm	73	2
25 mm	46	21
27 mm	29	44
29 mm	7	32
31 mm	0	8

Table 18
NYHA Classification

Class	Preoperative	14.6-yr Study
AORTIC		
I	3% (4/125)	72% (49/68)
II	42% (53/125)	27% (18/68)
III	42% (52/125)	2% (1/68)
IV	11% (14/125)	0%
Unknown	2% (2/125)	
MITRAL		
I	0%	80% (24/30)
II	10% (7/70)	10% (3/30)
III	67% (47/70)	10% (3/30)
IV	23% (16/70)	0%
DOUBLE (Aortic and Mitral)		
I	0%	41% (7/17)
II	3% (1/37)	41% (7/17)
III	92% (34/37)	18% (3/17)
IV	5% (2/37)	0%

Table 19
Hemodynamics:
Doppler Echocardiography Values of Mean Pressure Gradient and Effective Orifice Area
Mean \pm Standard Deviation [range] (sample size)

Size	Cardiac Output (L/min)	Mean Gradient (mmHg)	Effective Orifice Area (cm ²)
AORTIC			
21	7.50 \pm 1.80 [7.8] (2)	36 \pm 4 [32 - 41] (4)	1.30 \pm 0.10 [1.2 - 1.4] (3)
23	6.15 \pm 1.80 [2.5 - 10] (27)	19 \pm 8 [3.7 - 36] (40)	1.78 \pm 0.94 [0.9 - 5.49] (31)
25	6.42 \pm 1.92 [2.2 - 9] (11)	16 \pm 8 [3 - 30] (20)	1.92 \pm 0.84 [1 - 4.17] (15)
27	5.87 \pm 2.61 [3.59 - 8.9] (4)	12 \pm 4 [5.7 - 21] (14)	2.45 \pm 1.40 [0.95 - 4.4] (6)
29	— (0)	9 \pm 3 [7 - 13.7] (4)	— (0)
MITRAL			
25	4.26 \pm 1.13 [3.3 - 5.5] (9)	9 \pm 3 [5.3 - 16] (9)	1.70 \pm 0.39 [1.2 - 2.4] (9)
27	5.54 \pm 1.95 [3.2 - 9] (11)	5 \pm 3 [2.1 - 19.5] (23)	1.89 \pm 0.47 [1.4 - 3.4] (16)
29	6.50 \pm 1.85 [4.3 - 10] (7)	5 \pm 2 [2.5 - 7.8] (11)	1.64 \pm 0.17 [1.38 - 1.85] (8)
31	5.68 \pm 1.66 [3.97 - 9.0] (3)	6 \pm 2 [3.5 - 7.3] (3)	1.95 \pm 0.67 [1.4 - 2.69] (3)

Note: Sizes 27 and 29 mm have the same flow orifice dimensions (same disc/housing ring size), with only a larger suture ring making up the size difference. Similarly, sizes 31 and 33 have the same flow orifice dimensions, however, no size 33 mm valves were implanted in this study. The clinical

study (Section 10) did not generate sufficient data to support the safety and effectiveness of sizes 19, 21, 31, and 33 aortic valves and sizes 19-25 mitral valves.

Table 20
Hemodynamics:
Echocardiography Estimates of Valvular Regurgitation
 % of observations, # of cases/n

Valve Size	None	Trivial	Mild	Moderate	Severe	Undetermined
AORTIC	37%, 31/83	48%, 40/83	4%, 3/83	4%, 3/83	0	7%, 6/83
21	25%, 1/4	50%, 2/4	25%, 1/4	0	0	0
23	43%, 17/40	43%, 17/40	3%, 1/40	5%, 2/40	0	8%, 3/40
25	15%, 3/20	65%, 13/20	5%, 1/20	0	0	15%, 3/20
27/29	53%, 10/19	42%, 8/19	0	5%, 1/19	0	0
MITRAL	54%, 26/48	15%, 7/48	10%, 5/48	4%, 2/48	0	17%, 8/48
25	56%, 5/9	11%, 1/9	22%, 2/9	0	0	11%, 1/9
27/29	56%, 20/36	14%, 5/36	8%, 3/36	3%, 1/36	0	19%, 7/36
31/33	33%, 1/3	33%, 1/3	0	33%, 1/3	0	0

Note: The clinical study (Section 10) did not generate sufficient data to support the safety and effectiveness of sizes 19, 21, 31, and 33 aortic valves and sizes 19-25 mitral valves.

Echocardiography data also was obtained from another large foreign institution, separate from the 4-center clinical study, to further study hemodynamic characteristics of the Omnicarbon™ cardiac valve prosthesis. These data were collected at a mean postoperative time of 6.1 years for aortic valves and 5.3 years for mitral valves. Table 21 displays a summary of the estimated mean transvalvular gradient, effective orifice area, and cardiac output for each valve size.

Table 21
Hemodynamics from an Institution Outside the Clinical Study:
Doppler Echocardiography Values of Mean Pressure Gradient and Effective Orifice Area
 Mean ± Standard Deviation [range]

Size	n	Cardiac Output (L/min)	Mean Gradient (mmHg)	Effective Orifice Area (cm ²)
AORTIC				
21	6	4.60 ± 0.91 [3.40 - 5.81]	15 ± 11 [3-35]	1.40 ± 0.56 [0.62-2.27]
23	23	5.12 ± 1.31 [3.30 - 8.29]	14 ± 7 [3-36]	1.25 ± 0.24 [0.88-1.83]
25	75	4.97 ± 1.54 [2.50 - 8.90]	13 ± 5 [2-33]	1.53 ± 0.45 [0.72-2.92]
27	5	5.98 ± 1.85 [4.50 - 8.68]	10 ± 5 [4-17]	2.27 ± 0.99 [1.15-3.74]
29	2	5.12 [4.42, 5.82]	8 [8, 8]	1.55 [1.26, 1.83]
MITRAL				
27	26	4.69 ± 1.58 [2.65 - 8.73]	3 ± 1 [2-4]	2.63 ± 0.62 [1.61-4.31]
29	76	5.12 ± 1.48 [1.96 - 9.04]	3 ± 1 [1-9]	2.55 ± 0.73 [1.46-5.00]
31	9	4.90 ± 1.78 [2.59 - 8.29]	3 ± 1 [2-4]	2.88 ± 0.78 [1.69-4.06]

Note: The clinical study (Section 10) did not generate sufficient data to support the safety and effectiveness of sizes 19, 21, 31, and 33 aortic valves and sizes 19-25 mitral valves.

In addition to the echocardiography data, the applicant also presented catheterization data. Those data satisfied the quantity of data requested in the FDA Draft Guidelines of 1982 for sizes 21 – 29 mm aortic Omnicarbon™ valves and sizes 25 – 33 mm mitral valves.

11. CONCLUSIONS DRAWN FROM THE STUDIES

The results from pre-clinical laboratory studies performed on the Omnicarbon™ cardiac valve prosthesis for hydrodynamic performance testing and structural performance testing demonstrate that this device is suitable for long-term implant.

The animal studies demonstrate that the Omnicarbon™ cardiac valve prosthesis is safe for valve replacement.

Clinical results reported from a long-term clinical study provide reasonable assurance that the Omnicarbon™ cardiac valve prosthesis is safe and effective for replacement of dysfunctional native or prosthetic aortic or mitral valves.

12. PANEL RECOMMENDATIONS

In accordance with the provisions of Section 515(c)(2) of the Federal Food, Drug, and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, this PMA Supplement was not referred to the Circulatory Systems Device Panel, an FDA advisory committee, for review and recommendation, because the information in the PMA Supplement substantially duplicates information previously reviewed by this panel.

13. FDA DECISION

FDA issued an approval order on **JUL 26 2001**

The applicant's manufacturing and control facilities were inspected from May 25 – June 1, 2000, and the facility was found to be in compliance with the Quality System Regulation.

14. APPROVAL SPECIFICATIONS

Direction for Use: See final draft labeling (Instructions for Handling and Use).

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

Post-Approval Requirements and Restrictions: See approval order.