SUMMARY of SAFETY and EFFECTIVENESS DATA
MEDTRONIC HANCOCK® II
BIOPROSTHETIC HEART VALVE

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BIOPROSTHETIC HEART VALVE

1. General Information

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

Device Trade Name: .....Medtronic Hancock® II
Bioprosthetic Heart Valve

Applicant's Name and Address: .....Medtronic Heart Valves
.....7000 Central Avenue NE
.....Minneapolis, MN 55432

PMA Application Number: P980043
Date of Panel Recommendation: .....June 24, 1999
Date of Notice of Approval to the Applicant: .....

2. Indications For Use

Hancock II Bioprostheses (Models T505 and T510) are indicated for patients who require replacement of their native or prosthetic aortic and mitral valves.

3. Device Description

Hancock II Bioprostheses (Model T505, aortic, and Model T510, mitral) consist of porcine aortic valves which have been preserved in stabilized (0.2%) glutaraldehyde with a pressurized aortic root fixation process, and then fitted and secured to flexible acetal homopolymer stents. Hancock II Bioprostheses are treated with a surfactant, sodium dodecyl sulfate ("T6").

The Medtronic Hancock II Bioprostheses are designed for both the aortic position (Model T505) and mitral position (Model T510). They are available in the following implantation diameters:

- Model T505 - 21mm, 23mm, 25mm, 27mm and 29mm
- Model T510 - 25mm, 27mm, 29mm, 31mm and 33mm.

Testing has shown that the presence of this device (with the materials described) in a patient undergoing a MRI (magnetic resonance imaging) procedure using a MR system with a static magnetic field of <1.5 Tesla, will present no substantial or increased risk relative to magnetic field interactions, artifacts and/or heating.

4. Contraindications

None known

5. Warnings and Precautions

Warnings

FOR SINGLE USE ONLY.

DO NOT RESTERILIZE THE VALVE BY ANY METHOD. Exposure of the bioprosthesis and container to irradiation, steam, ethylene oxide or other chemical sterilants will render the bioprosthesis unfit for use.
WARNING. Accelerated deterioration due to calcific degeneration of bioprostheses may occur in:

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

5. PRECAUTIONS

Precautions Prior to Use

Do not use the Hancock II Bioprosthesis:

- if it has been exposed to freezing or has had prolonged exposure to heat.
- if the tamper evident seal is broken.
- if the glutaraldehyde storage solution does not completely cover the bioprosthesis.

Precautions During Use

- Do not expose to any solution except for the storage solution or sterile saline. Do not expose to antibiotics.
- Do not allow the valve tissue to dry. Maintain tissue moisture with irrigation or immersion in normal saline solution during surgery.
- Passage of a catheter, surgical instrument or transvenous pacing lead through the bioprosthesis may damage the valve.
- A replacement prosthesis should fit the native annulus snugly without over-distension.
- Avoid suture entanglement with the mitral stent posts and verify by examining the ventricular aspect of the implanted bioprosthesis.

6. Alternative Practices and Procedures

The alternative to the Medtronic Hancock II Bioprosthetic Heart Valve is surgical replacement of the malfunctioning aortic valve with a homograft or a stented bioprosthetic heart valve for which there is an approved premarket approval application (PMA). 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

Currently the device is distributed in Australia, Canada, Germany, UK, France, Spain, Italy, Belgium, Holland, Greece, Denmark, Finland, Sweden, Norway, Japan, Uruguay, Saudi Arabia, South Africa, Thailand, and Turkey.

The Medtronic Hancock II Bioprosthetic Heart Valve has never been withdrawn from distribution for any reason associated with the safety and/or the effectiveness of the device.

8. Adverse Events

Medtronic Long-Term Clinical Study
A multi-center evaluation was conducted that followed patients implanted with the Medtronic Hancock II Bioprosthesis, with patient follow-up out to 12 years for some patients. Two hundred sixty-seven (267) patients had isolated aortic valve replacement (AVR) and 102 patients had isolated mitral valve replacement (MVR). Patients were evaluated within 30 days of surgery, and on an annual basis through 1992. Since 1993, patients were evaluated once every other year. Adverse events were captured throughout the postoperative period.

Toronto Case Series
A case series of patients implanted with the Medtronic Hancock II Bioprosthesis was conducted, with patient follow-up out to 14 years for some patients. Seven hundred ten (710) patients had isolated aortic valve replacement (AVR) and 308 patients had isolated mitral valve replacement (MVR). Patients were implanted between September 1982 and December 1994. Patients were evaluated preoperatively, within 30 days of surgery, and at the following follow-up intervals: 1991, 1992-1993, 1994, and 1996. The first occurrence of device-related adverse events was captured (multiple events were not captured) throughout the postoperative period.

Observed Adverse Events

The tables below present early ($\leq$30 days for valve-related adverse events, $\leq$30 days or during hospitalization for death), linearized and cumulative freedom from adverse event rates. A linearized rate is not calculated for death, structural valve deterioration, nonstructural valve dysfunction, reoperation, and death, since these rates are not constant over time. The denominator used for calculation of the linearized rates was constant in the Medtronic Long-Term Clinical Study (it included only patient-years beyond 30 days), whereas the denominator in the Toronto Case Series varied because multiple events were not included.

Medtronic Long-Term Clinical Study: AVR

The adverse event rates were based on 267 bioprostheses implanted in 267 patients at seven centers. The cumulative follow-up was 1,889 patient-years with a mean follow-up of 7 years (SD=4 years, range=0 to 12 years).

Table 1: Observed Adverse Event Rates for AVR
Medtronic Long-Term Clinical Study

All patients analyzed: N=267 Cumulative follow-up=1,889 patient-years

Adverse Event	Early Events		Late Events[1]		Freedom from Event (%) [95% CI][2]		
	N	%	N	%/Pt.-Yr.	1 Year (n = 237)[3]	5 Years (n = 180)[3]	10 Years (n = 81)[3]
All Deaths	12	4.5	120	--	91.3 [87.9, 94.7]	72.3 [66.7, 77.9]	49.2 [41.6, 56.8]
Valve-Related or Unexplained	0	0	32	--	98.0 [96.2, 99.8]	92.9 [89.3, 96.5]	82.2 [74.6, 89.8]
Valve-Related Adverse Events							
Thromboembolism[4]	2	0.7	37	2.0	98.0 [96.2, 99.8]	92.9 [89.1, 96.7]	80.7 [72.1, 89.3]
Permanent Neurological Events	2	0.7	19	1.0	99.2 [98.0, 100.0]	96.7 [94.2, 99.2]	90.0[83.7, 96.3]
Transient Neurological Events	0	0	16	0.9	98.8 [97.4, 100.0]	96.7 [94.2, 99.2]	91.2 [84.7, 97.7]
Primary Valve Thrombosis	0	0	3	0.2	99.6 [98.8, 100.0]	98.7 [97.1, 100.0]	98.7 [96.2, 100.0]
Structural Valve Deterioration	0	0	11	--	100.0 [98.7, 100.0]	100.0 [98.3, 100.0]	94.4 [89.5, 99.3]
Nonstructural Valve Dysfunction[5]	0	0	2	--	99.6 [98.8, 100.0]	99.1 [97.7, 100.0]	99.1 [97.1, 100.0]
Endocarditis	3	1.1	12	0.6	98.0 [96.2, 99.8]	95.8 [92.9, 98.7]	93.0 [87.5, 98.5]
Periprosthetic Leak[6]	0	0	6	0.3	99.6 [98.8, 100.0]	98.5 [96.7, 100.0]	95.6 [91.1, 100.0]
Major Anticoagulant Related Hemorrhage	0	0	5	0.3	100.0 [98.7, 100.0]	99.5 [98.5, 100.0]	98.0 [95.0, 100.0]
Reoperation	0	0	23	--	98.8 [97.4, 100.0]	96.1 [93.3, 98.9]	89.6 [83.3, 95.9]
Explant	0	0	22	--	98.8 [97.4, 100.0]	96.6 [94.0, 99.2]	90.0 [83.8, 96.2]

Notes:

1. Late event rates were calculated as linearized rates (%/patient-year) based on 1,867.6 patient-years of follow-up (>30 days postoperative).
2. Freedom from event rates were calculated using the Kaplan-Meier method. Peto's formula was used for the calculation of the standard errors of these estimates for the confidence intervals for adverse events with at least one occurrence. For adverse events with no occurrences, the lower one-sided confidence limits were calculated as (1-maximum risk), where (1-maximum risk) = $(0.05)^{1/N}$, and N = number of patients remaining at risk.
3. Number of patients in study 1, 5, and 10 years after implant
4. Two late embolic events were in peripheral arteries.
5. Due to pannus
6. No events related to endocarditis

Medtronic Long-Term Clinical Study: MVR

The adverse event rates were based on 102 bioprostheses implanted in 102 patients at seven centers. The cumulative follow-up was 649 patient-years with a mean follow-up of 6 years (SD=4 years, range=0 to 12 years).

Table 2: Observed Adverse Event Rates for MVR
Medtronic Long-Term Clinical Study

All patients analyzed: N=102 Cumulative follow-up=649 patient-years

Adverse Event	Early Events		Late Events[1]		Freedom from Event (%) [95% CI][2]		
	N	%	N	%/Pt.-Yr.	1 Year (n = 82)[3]	5 Years (n = 65)[3]	10 Years (n = 26)[3]
All Deaths	13	12.7	48	--	81.3 [73.7, 88.9]	67.3 [57.9, 76.7]	38.1 [26.6, 49.6]
Valve-Related or Unexplained	2	2.0	16	--	94.6 [89.8, 99.4]	89.6 [82.6, 96.6]	77.4 [63.3, 91.5]
Valve-Related Adverse Events							
Thromboembolism[4]	3	2.9	20	3.1	94.6 [89.7, 99.5]	89.3 [81.9, 96.7]	73.0 [57.5, 88.5]
Permanent Neurological Events	1	1.0	9	1.4	97.9 [94.8, 100.0]	95.3 [90.2, 100.0]	85.8 [73.1, 98.5]
Transient Neurological Events	2	2.0	8	1.2	97.9 [94.8, 100.0]	95.1 [89.8, 100.0]	91.0 [79.8, 100.0]
Primary Valve Thrombosis	0	0	0	0	100.0 [96.4, 100.0]	100.0 [95.5, 100.0]	100.0 [89.1, 100.0]
Structural Valve Deterioration	0	0	7	--	100.0 [96.4, 100.0]	98.5 [95.6, 100.0]	90.7 [80.1, 100.0]
Nonstructural Valve Dysfunction[5]	0	0	0	--	100.0 [96.4, 100.0]	100.0 [95.5, 100.0]	100.0 [89.1, 100.0]
Endocarditis	0	0	5	0.8	100.0 [96.4, 100.0]	98.8 [96.1, 100.0]	94.6 [86.1, 100.0]
Periprosthetic Leak[6]	1	1.0	1	0.2	99.0 [96.8, 100.0]	97.5 [93.7, 100.0]	97.5 [91.5, 100.0]
Major Anticoagulant Related Hemorrhage	0	0	7	1.1	100.0 [96.4, 100.0]	95.8 [90.9, 100.0]	89.8 [78.6, 100.0]
Reoperation	0	0	8	--	100.0 [96.4, 100.0]	98.5 [95.6, 100.0]	88.5 [77.0, 100.0]
Explant	0	0	8	--	100.0 [96.4, 100.0]	98.5 [95.6, 100.0]	88.5 [77.0, 100.0]

Notes:

1. Late event rates were calculated as linearized rates (%/patient-year) based on 641.0 patient-years of follow-up (>30 days postoperative).
2. Freedom from event rates were calculated using the Kaplan-Meier method. Peto's formula was used for the calculation of the standard errors of these estimates for the confidence intervals for adverse events with at least one occurrence. For adverse events with no occurrences, the lower one-sided confidence limits were calculated as (1-maximum risk), where (1-maximum risk) = $(0.05)^{1/N}$, and N = number of patients remaining at risk.
3. Number of patients in study 1, 5, and 10 years after implant
4. Three late embolic events were in peripheral arteries.
5. Due to pannus
6. No events related to endocarditis

Toronto Case Series: AVR

The adverse event rates were based on 710 bioprostheses implanted in 710 patients at The Toronto Hospital. The cumulative follow-up was 4,064 patient-years with a mean follow-up of 6 years (SD=3 years, range=0 to 14 years).

Table 3: Observed Adverse Event Rates for AVR
Toronto Case Series
All patients analyzed: N=710 Cumulative follow-up=4,064 patient-years

Adverse Event	Early Events		Late Events		Freedom from Event (%) [95% CI][1]		
	N	%	N	%/Pt.-Yr.	1 Year (n = 648)[2]	5 Years (n = 398)[2]	10 Years (n = 80)[2]
All Deaths	34	4.8	156	--	92.5 [90.5, 94.5]	80.3 [76.8, 83.8]	63.4 [55.0, 71.8]
Valve-Related or Unexplained	--	--	18	--	99.9 [99.7, 100.0]	97.9 [96.5, 99.3]	95.9 [91.6, 100.0]
Valve-Related Adverse Events							
Thromboembolism	6	0.8	48	1.2	98.2 [97.2, 99.2]	94.3 [92.0, 96.6]	86.7 [79.4, 94.0]
Permanent Neurological Events	5	0.7	34	0.9	98.7 [97.8, 99.6]	95.8 [93.8, 97.8]	90.5 [84.3, 96.7]
Transient Neurological Events	1	0.1	14	0.4			
Primary Valve Thrombosis[3]	0	0	0	0	100.0 [99.5, 100.0]	100.0 [99.3, 100.0]	100.0 [96.3, 100.0]
Structural Valve Deterioration[3]	0	0	10	--	100.0 [99.5, 100.0]	99.6 [99.0, 100.0]	95.4 [90.9, 99.9]
Endocarditis	1	0.1	17	0.4	99.4 [98.8, 100.0]	97.8 [96.4, 99.2]	96.2 [92.1, 100.0]
Major Periprosthetic Leak[3]	0	0	3	0.1	99.9 [99.7, 100.0]	99.9 [99.6, 100.0]	99.0 [96.8, 100.0]
Reoperation	0	0	24	--	99.4 [98.8, 100.0]	97.7 [96.2, 99.2]	93.0 [87.6, 98.4]
Explant	0	0	23	--	99.4 [98.8, 100.0]	97.8 [96.4, 99.2]	93.2 [87.9, 98.5]

Notes:

1. Freedom from event rates were calculated using the Kaplan-Meier method. Peto's formula was used for the calculation of the standard errors of these estimates for the confidence intervals for adverse events with at least one occurrence. For adverse events with no occurrences, the lower one-sided confidence limits were calculated as (1-maximum risk), where (1-maximum risk) = $(0.05)^{1/N}$, and N = number of patients remaining at risk.
2. Number of patients in case series 1, 5, and 10 years after implant
3. Resulting in reoperation or death

Toronto Case Series: MVR

The adverse event rates were based on 308 bioprostheses implanted in 308 patients at The Toronto Hospital. The cumulative follow-up was 1720 patient-years with a mean follow-up of 6 years (SD=4 years, range=0 to 14 years).

Table 4: Observed Adverse Event Rates for MVR
Toronto Case Series
All patients analyzed: N=308 Cumulative follow-up=1,720 patient-years

Adverse Event	Early Events		Late Events		Freedom from Event (%) [95% CI][1]		
	N	%	N	%/Pt.-Yr.	1 Year (n = 269)[2]	5 Years (n = 159)[2]	10 Years (n = 43)[2]
All Deaths	24	7.8	89	--	88.3 [84.7, 91.9]	72.9 [67.0, 78.8]	53.5 [42.6, 64.4]
Valve-Related or Unexplained	--	--	17	--	99.6 [98.8, 100.0]	95.9 [92.9, 98.9]	88.8 [79.9, 97.7]
Valve-Related Adverse Events							
Thromboembolism	1	0.3	17	1.0	99.3 [98.3, 100.0]	94.9 [91.5, 98.3]	90.3 [81.8, 98.8]
Permanent Neurological Events	1	0.3	15	0.9	99.3 [98.3, 100.0]	95.5 [92.3, 98.7]	91.6 [83.6, 99.6]
Transient Neurological Events	0	0	2	0.1	--	--	--
Primary Valve Thrombosis[3]	0	0	1	0.1	100.0 [98.9, 100.0]	100.0 [98.1, 100.0]	99.3 [96.8, 100.0]
Structural Valve Deterioration[3]	0	0	16	--	100.0 [98.9, 100.0]	100.0 [98.1, 100.0]	83.9 [73.8, 94.0]
Endocarditis	0	0	10	0.6	98.9 [97.7, 100.0]	96.1 [93.1, 99.1]	95.3 [89.1, 100.0]
Major Periprosthetic Leak[3]	0	0	2	0.1	100.0 [98.9, 100.0]	99.1 [97.6, 100.0]	99.1 [96.3, 100.0]
Reoperation	0	0	21	--	99.3 [98.3, 100.0]	98.4 [96.5, 100.0]	82.3 [72.0, 92.6]
Explant	0	0	20	--	99.7 [99.0, 100.0]	98.8 [97.1, 100.0]	82.6 [72.3, 92.9]

Notes:

1. Freedom from event rates were calculated using the Kaplan-Meier method. Peto's formula was used for the calculation of the standard errors of these estimates for the confidence intervals for adverse events with at least one occurrence. For adverse events with no occurrences, the lower one-sided confidence limits were calculated as (1-maximum risk), where (1-maximum risk) = $(0.05)^{1/N}$, and N = number of patients remaining at risk.
2. Number of patients in case series 1, 5, and 10 years after implant
3. Resulting in reoperation or death

9. Summaries of Non-clinical Studies

9.1 Bench Testing

In vitro tests performed were initially done for the original Medtronic Hancock II PMA (P850042), submitted in 1985 and amended in 1992 (P900028). The October 1986 FDA Heart Valve Guidance was used as the basis for the tests and methodologies used for these initial studies.

The initial in vitro tests were performed in conformance with the current (1994) FDA Heart Valve Guidance and were found acceptable except for tests pertaining to fatigue, dynamic failure mode and stent creep. Subsequent testing done on the Medtronic Mosaic® Bioprosthetic Heart Valve, which has the same stent and stent covering as the Hancock II valve, was performed and found acceptable.

9.1.1 Biocompatibility, Immunology and Toxicology Studies

The biocompatibility tests which were performed meet the requirements of the Initial Evaluation Tests, ISO 10993-1, with the exception of sub-chronic toxicity. A matrix of the tests performed is provided in Table 5.

Table 5: Biocompatibility Tests and Results

Test Performed	Samples: Hancock II	Samples Control	Test Objective/ Pass/Fail Criteria	Results
Cage Implant Studies Study Duration: 4, 7 and 14 days. Lab: Departments of Macromolecular Science and Pathology. Case Western University. GLP Status - No	T6-Treated Leaflets and Delrin	Empty Cage	Determination of cellular response during acute & chronic inflammation over time caused by the material in terms of leukocyte counts, intracellular & extracellular enzyme activities.	Test samples performed suitably (i.e. do not elicit an in vivo inflammatory response
Cytotoxicity: "Cytotoxicity Study Using the Elution Method in the L-929 Mouse Fibroblast Cell Line" Duration: 24 hours. Lab: Physiological Research Laboratory GLP Status - No	Delrin, Dacron	Negative Control: Silicone rubber tubing. Positive Control: Amber latex glove.	Determine the degree of morphologically discernible cytotoxicity by examining cells microscopically.	Test samples performed suitably

Test Performed	Samples: Hancock II	Samples Control	Test Objective/ Pass/Fail Criteria	Results
Static Hemolysis Test Rabbit red blood cells (RRBC) Duration: 90 minutes @ 37° C Lab: Physiological Research Laboratory GLP Status - Yes	Delrin	Negative Control: Silicone rubber tubing. Positive Control: Amber latex glove.	Determine degree of hemolysis of red cells caused by exposure to test material. Material is non-hemolytic if percentage of hemolysis is ≤ 5%.	Test samples performed suitably (i.e. was non-hemolytic)
USP Acute Intracutaneous Injection Test "Acute Intracutaneous Reactivity Study in the Rabbit" Duration: 24, 48, and 72 hours. Lab: NAMSA GLP Status - No	Delrin, Dacron	Negative Control: Cottonseed oil, NaCl Injection Positive Control: None	Observation of injection sites for erythema and edema at 24, 48 & 72 hours after cottonseed oil and saline extracts of test material.	Test samples performed suitably
USP Acute Systemic Injection Test "Acute Systemic Study in the Mouse" Duration: 4, 24, 48, and 72 hours. Lab: NAMSA GLP Status - No	Delrin, Dacron	Negative Control: Cottonseed oil NaCl Injection Positive Control: None	Observation of test animals following intravenous injections of saline extracts of test material and intraperitoneal injection of cottonseed oil extracts of test material.	Test samples performed suitably
Mutagenicity: Ames Test "Ames Salmonella/Mammalian" Duration: 5 day. Lab: Nelson Laboratories GLP Status - Yes	T6-Treated Valves and Delrin	Positive Control: Sodium Azide, 4-nitro-0-phenylenediamine (NPD), and 2 aminofluorene (2AF)	Determine if the materials are mutagenic by testing extracts using the salmonella/mammalian microsome mutagenicity assay.	Test samples performed suitably
USP Pyrogen Test "Rabbit Pyrogen Study" Duration: 1, 2, and 3 hours post injection. Lab: United States Testing Company GLP Status - Yes LAL Testing	T-6 Treated Valves finished	(No control required) Saline extract of test material.	Determine if the extracts of T-6 treated valves and T-6 are chemical mediators of Pyrogenicity. IV infusion of extract shall not cause rise of rabbit	Test samples performed suitably Test samples performed

Test Performed	Samples: Hancock II	Samples Control	Test Objective/ Pass/Fail Criteria	Results
(performed monthly) Duration: one hour Lab: Medtronic Heart Valves GLP Status - No	product	No control	body temperature of 0.6°C. Determine that endotoxin levels are <0.5 ng/ml.	suitably
Sensitization: Kligman Test "Skin Sensitization in Guinea Pig by Kligman (Maximization Method)" Duration: Induction Regime: Injection at day 0; Topical occluded patch for 48 hours and 7 days. Challenge Regime: Topical occluded patch 24 hour exposure on day 14. Dermal Reaction readings: 0, 1, 24, and 48 hour post challenge doses. Lab: United States Testing Company, Inc. GLP Status - Yes	Delrin	Saline and cottonseed oil extracts of test material. (No control required)	Evaluate the potential to elicit a delayed-contact dermal sensitization response (erythema and /or edema) in test animals.	Test samples performed suitably
Subchronic Toxicity			Cage studies showed no short-term toxic effects. Since the probability of toxicity is greater short-term, subchronic toxicity tests were not considered necessary.	
Health Risk Assessment Duration: 0 - 72 hour extraction Lab: J.B. Stevens & Associates/Pace Laboratories GLP Status - N/A	T-6 Treated Valves	N/A	Evaluate the potential health risk to patients due to the presence of residual glutaraldehyde in the valve. Residuals must be at non-toxic levels.	Test samples performed suitably

The Hancock II bioprosthesis stent contains an annular ring and eyelet markers of Haynes Alloy #25. This material has a history of use as an implantable material and a documented history of biocompatibility.

The results of these studies and evaluations showed all components of the Hancock II Bioprosthetic Heart Valve to be biocompatible.

9.1.2 Hydrodynamic Performance

All data in this section were obtained from valve samples, including control valves used in these tests, that were final production models.

Tests were conducted at ambient temperature in normal saline. The steady flow rate pressure drop testing was performed at a flow rate range of 5 to 30 L/min for both the aortic and mitral valves, with an accuracy ±0.5 mmHg. The pulsatile flow pressure drop testing was performed at a cardiac output range of 2.5 to 7.5 L/min for both the aortic and mitral valves, with an accuracy of ±0.5 mmHg. The pulsatile flow pressure drop testing was done at a pulse rate of 70 bpm, with systole accounting for approximately 35% of the simulated cardiac cycle.

The data obtained from the hydrodynamic testing of the Hancock II bioprosthesis show the steady and pulsatile flow pressure drop, regurgitation, back pressure leakage and flow characteristics are acceptable and similar to those of other, commercially released bioprosthetic heart valves. The test and results are summarized in Table 6.

Table 6: Hydrodynamic Testing and Results

TEST	SAMPLE SIZE: HANCOCK II	SAMPLE SIZE: CONTROL (Hancock Std)	PASS/FAIL CRITERIA	RESULTS
Steady Forward Flow Pressure Drop	3 each size & type	1 - 27 A 1 - 27 M	Pressure drop ≤ control valve	Pass
Backflow Leakage Testing	3 each size & type	1 - 25 A 1 - 29 M	Leakage volume ≤ control valve	Pass
Pulsatile Flow Pressure Drop	3 each size & type	1 - 27 A 1 - 27 M	Pressure drop ≤ control valve	Pass
Pulsatile Flow Regurgitation	1 each size & type	1 - 25 A 1 - 29 M	Regurgitant volume ≤ control valve	Pass
Flow Visualization	1 - 27 A 1 - 27 M	N/A	Similar to valves currently in clinical use	Pass

Note: N/A = not applicable

9.1.3 Structural Performance

Testing was performed on Hancock II valves, and appropriate control valves, to determine the structural performance of the Hancock II valve. The tests included accelerated wear, fatigue, dynamic failure mode, stent creep and stent deflection. In addition, the initial Hancock II in vitro tests were performed using the guidance in the current (1994) FDA Heart Valve Guidance and

found acceptable, except for tests pertaining to fatigue, dynamic failure mode and stent creep. To support the original tests, data were taken from testing performed on the Medtronic Mosaic Bioprosthetic Heart Valve, which has the same stent as the Hancock II bioprosthesis. Absorption and adsorption data, relative to the Hancock II stent, were also taken from the Mosaic test data. The results of the structural performance tests are summarized in Table 7.

Table 7: Structural Performance Tests and Results

TEST	SAMPLE SIZE: HANCOCK II	SAMPLE SIZE: CONTROL	PASS/FAIL CRITERIA	RESULTS
Accelerated Wear Testing	3 each size and type 6 largest A and M	1 - 25 A Hnck Std 1 - 27 M Hnck Std 2 - A Hnck II non T6 treated valves 2 - M Hnck II non T6 treated valves	Test and control valves to exhibit similar results at end of the test	No valves exhibited evidence of change in coaptation or cusp shape. No evidence of stent creep or deformation. All valves functioned normally at end of test.
Fatigue – Delrin Material Properties	Per ASTM and Medtronic procedures	Per ASTM and Medtronic procedures	Assessment: Determine that the Delrin stent material will maintain its structural integrity through the mfg. process, throughout the shelf life of the valve and in vivo.	Mechanical properties of Delrin, measured in a dry and wet (processing and packaging solutions) state, were stable at the end of the mfg. process. Tensile, flexural and fatigue properties of wet Delrin did not change with time (6 years or twice the shelf life). Crystallinity of Delrin did not change due to mfg. or due to long-term exposure to packaging solution.
Fatigue – Fracture Mechanics Fatigue – Fracture	Thirteen test samples per ASTM E647	N/A	Assessment: Determine the fatigue crack growth rates for Delrin and the sensitivity of the Hancock II stent to failure due to crack initiation & propagation.	Fatigue crack growth rates agree with published data for polyacetal. Cycle rate does not affect the Delrin fatigue growth rate in a pseudo in vivo environment. There was no aging time or temp. effect on the fatigue crack growth rates. Failure defect size (at hypertensive pressure) was more than half the stent rail width. Maximum defect size

TEST	SAMPLE SIZE: HANCOCK II	SAMPLE SIZE: CONTROL	PASS/FAIL CRITERIA	RESULTS
Mechanics (Continued)				(worst-case stent to ensure no crack growth, 175 mmHg) is 0.026 inch.
Fatigue – Finite Element Analysis	Each size and type of Hancock II valve.	N/A	Assessment: Identify peak stresses in each Hancock II valve stent size and type. Identify the stent with the highest stress.	The peak stresses, identified for the aortic and mitral stents, ranged from 806 psi to 2266 psi (tensile) and from 1269 psi to 2945 psi (compressive). The stent with the highest stress was the 31 M.
Fatigue – Fatigue Lifetime Analysis	≥ 3 stents each size and type.	N/A	Assessment: Define the fatigue lifetime of Hancock II stents and associated safety margins.	There was no difference in fatigue resistance of fresh stents vs. stents from valves beyond 3 year shelf life. Worst-case safety factors (normal & hypertensive conditions) were 3.6 & 2.5. Hancock II stents will last beyond 15 years in vivo, even in patients with protracted, extreme pathological hypertension.
Dynamic Failure Mode	One each size and type .	1 - 25 A Hnck Std. 1 - 27 M Hnck Std. 1 - 25 A Hnck II non-T6 treated. 1 - 27 M Hnck II non-T6 treated	Assessment: Determine ultimate failure mode of the Hancock II valve.	All valves failed due to incompetence. No stent breakage resulted from this test. Reference valves sustained cycles to failure similar to the test valves. After the equivalent of 5 years physiologic pressure, the Hnck II valve can sustain cyclic pressures at least two times higher than an extreme hypertensive pressure (250 mmHg) without failure
Sewing Ring Integrity	N/A	N/A	Assessment: Determine mechanical integrity of the sewing ring.	Testing was not required by 1986 Heart Valve Guidance and was not done. Since there is over 13 years clinical experience with the Hancock II valve, this testing was not

TEST	SAMPLE SIZE: HANCOCK II	SAMPLE SIZE: CONTROL	PASS/FAIL CRITERIA	RESULTS
				deemed necessary.
Stent Creep	≥ 2 largest A & M stents, worst-case stent (31 M)	N/A	Assessment: Determine the dynamic creep characteristics of the Hancock II valve.	Creep stabilization occurred in less than two weeks. Only primary and secondary creep was observed. No tertiary creep was evident. Creep of worst-case stent after 10 years in a hypertensive patient (simulated) produced a negligible increase in the valve pressure drop.
Stent Deflection	At least 3 of each size and type of Hancock II stents. (Total of 54)	N/A	Assessment: Determine stent commissure post deflections at various valve pressure drops.	The elastic strain of the Hancock II stent is linear with closed valve pressure drop, independent of increasing or decreasing pressures.
Supporting Structural Testing (Based on testing of the Mosaic stent, which is the same as the Hancock II stent.)	As defined in specific test procedures.	As defined in specific test procedures.	Assessment: 1) Use Mosaic stent in vitro test data to support Hancock II data relative to: finite element analysis, fatigue lifetime analysis, dynamic failure mode and stent creep. 2) Determine absorption and adsorption properties of the Hancock II stent.	1) The results of the finite element analysis, fatigue lifetime analysis, dynamic failure mode and stent creep for the Mosaic stent supported the results of the testing done on the Hancock II stent. 2) Delrin is a suitable material for use in a physiological environment. It was not significantly altered chemically, dimensionally by aqueous solutions. Nor were its physical properties altered.

Note: N/A - not applicable

9.2 Animal Studies

An animal study (sheep model) was performed to evaluate the hemodynamic performance and valvular pathology of the Hancock II heart valve, as well as the efficacy of the T6 (sodium dodecyl sulfate) antimineralization treatment. The sheep model was chosen because untreated bioprosthetic heart valves in this animal model usually undergo accelerated calcification. The

study was performed using weanling sheep weighing 21-36 kg (mean 25 kg) at implant. Seven aortic Hancock II bioprosthetic valves (21-23 mm), treated with T6, were implanted in the mitral position. Aortic valves were implanted in lieu of mitral valves due to the sizes available for mitral valves (25-33 mm) and the natural anatomical requirements of the sheep (21-23mm) in the size range required for the studies. All valves were of clinical quality.

The mean implant time was 15.6 weeks with a range of 13.3-19.1 weeks. Six of the seven sheep survived the implant and were selectively terminated. One operative death occurred due to complications arising from the cardiopulmonary bypass procedure.

The mean transvalvular gradients for the animals ranged from 5.8 to 15.3 mmHg at cardiac outputs of 1.6 to 3.2 L/min. The ventriculograms demonstrated all six valves were completely competent.

All valves appeared to be healed in the sewing ring area and covered with a neointimal layer. No stent post distortion, valvular perforations, or torn leaflets were observed. None of the "long-term" valves exhibited gross thrombi, nor was there evidence of thromboembolic complications.

The gross and histological findings revealed some fibrous sheathing, a characteristic finding of tissue valves implanted in young growing animals. Its formation on the inflow side of the leaflet probably prevented full leaflet opening--hence, the higher than expected pressure gradients. There was one perivalvular leak which may have resulted from the aortic valve's scalloped sewing ring design being applied to the flat mitral annulus. Significant calcification was not observed in any of the valves.

9.3 Sterilization

The Medtronic Hancock II Bioprosthetic Heart Valve is sterilized in a 0.2% glutaraldehyde solution with placement of the packaged valve assembly into an incubator for terminal sterilization at 38°C - 42°C for 20-22 hours. After completion of terminal sterilization the product is held in quarantine until sterility is verified in accordance with process specifications. Annual requalification of the sterilization process is performed.

9.4 Shelf Life

The package integrity for the Hancock II Heart Valves was qualified for a three year shelf life through package integrity testing conducted for the FREESTYLE® Aortic Root Bioprosthesis. This testing is directly applicable to Hancock II since the jar/lid/seal assembly is identical for the two product lines. The Freestyle package assembly, which includes the tissue valve within a retainer, is considered worst-case. The valve retainer contained within the jar/lid/seal assembly has greater mass (~42g for Freestyle versus 15g for Hancock II) and thus can reasonably be concluded to have a greater impact on the jar/lid/seal during shipping/handling.

The Freestyle package integrity testing included a vacuum leak test, lid removal torque test, solution volume check test and a microbial challenge. Prior to integrity testing, the package

underwent three sterilization cycles (process parameters are identical to Hancock II), environmental stress conditioning, accelerated aging, and shipping/handling testing. Although the Hancock II manufacturing process allows for the sterilization process to be repeated for a total of six cycles, the thermal stressing of the Freestyle package assemblies prior to integrity testing can be considered worst-case. Along with the three sterilization cycles (each cycle: 24 hr & 41 $\pm$1° C) that were performed, the high temperature portion of the environmental stress conditioning created thermal stress conditions (72 hr @ 40$\pm$2° C) which are considered to be equivalent to a sterilization cycle in terms of temperature differential. In addition, the accelerated aging of the package assemblies included two thermal stressing cycles which significantly exceeded the temperature which is seen by the packages during a sterilization cycle (~57° C versus ~41° C). Thus, the package assemblies were exposed to six high temperature thermal stressing cycles which were equivalent to or exceeded, in temperature differential, thermal stress conditions which would be experienced by the package assemblies in six sterilization cycles.

Testing was conducted to ensure that product integrity had been maintained after real time aging to three years. The product integrity testing included tests that were designed to affirm the functionality of the valve through the examination of multiple aspects of valve performance and structure. The qualification included: shrink temperature (10 aged samples, 10 non-aged samples), collagen content (enzyme susceptibility; 10 aged samples, 10 non-aged samples), moisture content (10 aged samples, 10 non-aged samples), hydrodynamic performance (3 aged samples 19/23/27 mm, 1 non-aged control), biaxial mechanical (7 aged valves, 7 non-aged valves), histological evaluation (3 aged test valves 19/23/27 mm, 1 non-aged control), storage solution pH (15 samples) and glutaraldehyde percentage (15 samples). All test samples were real-time aged to three years, and underwent environmental stress conditioning before tests were conducted.

The acceptance criteria were met for all tests. Therefore, the Hancock II Heart Valve and its packaging are considered to be qualified for a three year shelf life.

10. Summaries of Clinical Studies

The safety endpoints captured in the studies were complications, and effectiveness endpoints were New York Heart Association (NYHA) functional classification and echocardiographic assessments. Also captured were patient demographics. These are presented in the tables below.

Table 8: Patient Demographics

Medtronic Long-Term AVR Clinical Study (N = 267)	
Age at implant in years (mean ± SD, [min., max.])	64 ± 14, [17, 86]
Gender (% male / % female)	79% / 21%
Etiology	
Stenosis- % of pts. with stenosis alone (% [number in subgroup/N])	58% (154/267)
Insufficiency- % of pts. with insufficiency alone (% [number in subgroup/N])	23% (62/267)
Mixed-% of pts. with stenosis and insufficiency (% [number in subgroup/N])	19% (51/267)
Medtronic Long-Term MVR Clinical Study (N = 102)	
Age at implant in years (mean ± SD, [min., max.])	63 ± 11, [26, 85]
Gender (% male / % female)	52% / 48%
Etiology	
Stenosis- % of pts. with stenosis alone (% [number in subgroup/N])	21% (21/102)
Insufficiency- % of pts. with insufficiency alone (% [number in subgroup/N])	65% (66/102)
Mixed-% of pts. with stenosis and insufficiency (% [number in subgroup/N])	15% (15/102)
Toronto Case Series AVR (N = 710)	
Age at implant in years (mean ± SD, [min., max.])	65 ± 12, [18, 86]
Gender (% male / % female)	75% / 25%
Etiology	
Stenosis- % of pts. with stenosis alone (% [number in subgroup/N])	46% (325/710)
Insufficiency- % of pts. with insufficiency alone (% [number in subgroup/N])	24% (170/710)
Mixed-% of pts. with stenosis and insufficiency (% [number in subgroup/N])	30% (211/710)
UNKNOWN	<1% (4/710)
Toronto Case Series MVR (N = 308)	
Age at implant in years (mean ± SD, [min., max.])	65 ± 11, [22, 86]
Gender (% male / % female)	44% / 57%
Etiology	
Stenosis- % of pts. with stenosis alone (% [number in subgroup/N])	19% (59/308)
Insufficiency- % of pts. with insufficiency alone (% [number in subgroup/N])	61% (188/308)
Mixed-% of pts. with stenosis and insufficiency (% [number in subgroup/N])	19% (59/308)
Unknown	<1% (2/308)

Table 9: Effectiveness Outcomes, Functional NYHA

NYHA Class	Preoperative		Latest	
	n/N	%	n/N	%
Medtronic Long-Term AVR Clinical Study (N = 267)				
I	5/267	2%	131/257	51%
II	55/267	21%	50/257	20%
III	169/267	63%	24/257	9%
IV	37/267	14%	9/257	4%
Unknown	1/267	<1%	43/257	17%
Medtronic Long-Term MVR Clinical Study (N = 102)				
I	0/102	0%	33/90	37%
II	11/102	11%	20/90	22%
III	71/102	70%	17/90	19%
IV	18/102	18%	5/90	6%
Unknown	2/102	2%	15/90	17%
Toronto Case Series AVR (N = 710)				
I	19/710	3%	294/489	60%
II	163/710	23%	135/489	28%
III	306/710	43%	58/489	12%
IV	222/710	31%	2/489	<1%
Unknown	0/710	0%	0/489	0%
Toronto Case Series MVR (N = 308)				
I	6/308	2%	70/172	41%
II	22/308	7%	66/172	38%
III	126/308	41%	35/172	20%
IV	154/308	50%	1/172	1%
Unknown	0/308	0%	0/172	0%

Note: Latest assessment in the Medtronic Long-Term Clinical Study ranged from 1984 through 1996. Latest assessment in the Toronto Case Series was in 1996.

Table 10: Effectiveness Outcomes, Toronto Case Series, Hemodynamics Aortic Valve Replacement

Valvular Regurgitation	% (n/N)
0 (none)	77% (158/205)
1+ (trace/trivial/mild)	15% (31/205)
2+ (mild/moderate)	2% (4/205)
3+ (moderate/severe)	0% (0/205)
4+ (severe)	0% (0/205) 6%
Unknown	(12/205)

Mean Pressure Gradient (mmHg)	Number in subgroup/N, mean ± SD [min., max.]
21 mm	9/13, 12.9 ± 4.2 [6.0, 19.2]
23 mm	47/53, 13.2 ± 4.6 [4.8, 26.1]
25 mm	50/60, 11.3 ± 4.4 [2.1, 26.0]
27 mm	48/57, 11.7 ± 4.8 [4.0, 24.0]
29 mm	19/22, 10.5 ± 3.6 [5.3, 19.2]

Note: Studies performed on 205 patients through 5 years postoperatively. Data not available for 32 patients.

Effective Orifice Area (cm^2)	Number in subgroup/N, mean ± SD [min., max.]
21 mm	11/13, 1.4 ± 0.5 [0.8, 2.4]
23 mm	48/53, 1.3 ± 0.2 [0.9, 1.9]
25 mm	50/60, 1.4 ± 0.3 [0.9, 2.3]
27 mm	47/57, 1.6 ± 0.4 [0.9, 2.5]
29 mm	19/22, 1.4 ± 0.3 [1.0, 2.3]

Note: Studies performed on 205 patients through 5 years postoperatively. Data not available for 30 patients.

Table 11: Effectiveness Outcomes, Toronto Case Series, Hemodynamics Mitral Valve Replacement

Valvular Regurgitation	% (n/N)
0 (none)	71% (92/130)
1+ (trace/trivial/mild)	22% (29/130)
2+ (mild/moderate)	2% (3/130)
3+ (moderate/severe)	0% (0/130)
4+ (severe)	0% (0/130)
Unknown	5% (6/130)

Mean Pressure Gradient (mmHg)	Number in subgroup/N, mean ± SD [min., max.]
25 mm	0/2
27 mm	8/25, 4.5 ± 2.5 [2.3, 10.0]
29 mm	8/33, 4.1 ± 1.6 [2.0, 6.0]
31 mm	8/55, 3.8 ± 1.8 [2.0, 6.0]
33 mm	1/15, 3.0 [3.0, 3.0]

Note: Studies performed on 130 patients through 5 years postoperatively. Data not available on 105 patients.

Effective Orifice Area (cm^2)	Number in subgroup/N, mean ± SD [min., max.]
25 mm	1/2, 4.5 [4.5, 4.5]
27 mm	20/25, 2.5 ± 0.8 [1.2, 4.6]
29 mm	33/33, 2.7 ± 0.6 [1.4, 4.2]
31 mm	49/55, 2.6 ± 0.7 [1.2, 5.0]
33 mm	15/15, 3.0 ± 0.9 [1.0, 4.4]

Note: Studies performed on 130 patients through 5 years postoperatively. Data not available on 12 patients.

The following tables summarize results of explant analyses performed on the Hancock II valve.

Table 12: Summary of Calcium Grading[1] (Medtronic)

Severity of Calcium by X-ray	# Aortic Valves	# Mitral Valves	# Tricuspid Valves	Total # Valves	Age range at Implant (Years)	Implant Duration Range (Months)	Distribution of Clinical Reason for Removal[2]							
							SVD	THR	INC	PAN	PPL	MR	MS	DTH
0	15	9	0	24	26-80	0-104	5	7	5	1	1	1	0	4
<1+	2	3	0	5	43-71	15-114	2	0	0	1	1	0	0	1
1+[3]	3	8	1	12	23-71	32-126	7	0	1	2	0	1	1	0
2+	3	1	0	4	18-66	67-125	4	0	0	0	0	0	0	0
3+	0	0	0	0	--	--	0	0	0	0	0	0	0	0
4+	2	1	0	3	34-63	25-139	3	0	0	0	0	0	0	0
Total	25	22	1	48	18-80	0-139	21	7	6	4	2	2	1	5

Notes:
1. Valves with endocarditis are not included in this table.
2. SVD=Structural valve deterioration
   THR=Thrombus
   INC=Incidental valve replacement
   PAN=Pannus overgrowth
   PPL=Periprosthetic leak
   MR=Mitral regurgitation
   MS=Mitral stenosis
   DTH=Death
4. Two valves were removed from one patient.

Table 13: Summary of Calcium Grading[1] (Toronto Case Series)

Severity of Ca++ by X-ray	No. Aortic Valves	No. .Mitral Valves	No. Tricuspid Valves	Total No. Valves	Age at Implant (Years) Range	Implant Duration (Months) Range	Distribution of Clinical Reason for Removal[2]					
							SVD	THR	INC	PAN	PPL	DTH
0	12	3	0	15	31-74	0-96	3	0	4	0	2	6
<1+	1	3	0	4	39-75	95-120	3	0	1	0	0	0
1+	2	3	0	5	27-70	59-117	5	0	0	0	0	0
2+	2	1	0	3	32-54	85-134	3	0	0	0	0	0
3+	2	0	0	2	32-41	65-139	2	0	0	0	0	0
4+	0	1	0	1	64	91	1	0	0	0	0	0
Total[3]	19	11	0	30	27-75	0-139	17	0	5	0	2	6

Notes:
1. Valves with endocarditis are not included in this table.
2. SVD=Structural valve deterioration
   THR=Thrombus
   INC=Incidental valve replacement
   PAN=Pannus overgrowth
   PPL=Periprosthetic leak
   DTH=Death
3. No calcium grading for four valves

10.1. Description of Patients and Analysis for Gender Bias

A gender bias was not noted in the Medtronic Long-Term Clinical Study and the Toronto Case Series.

For AVR, 79% of the patients in the Medtronic Long-Term Clinical Study and 75% of the patients in the Toronto Case Series were male. For MVR, 52% of the patients in the Medtronic Long-Term Clinical Study and 44% of the patients in the Toronto Case Series were male. Gender distribution is consistent with the incidence of disease in the U.S. and Canada. Based on an evaluation of valve-related adverse events following AVR for patients in the Medtronic Long-Term Clinical Study and patients in the Toronto Case Series, the freedom from valve-related adverse event rates were similar for men and women, except for endocarditis. In the Medtronic Long-Term Clinical Study, all cases of endocarditis occurred in male patients. However, in the Toronto Case Series, freedom from endocarditis was similar for men and women. Therefore, the results for valve-related adverse events following AVR presented in the analyses are representative for both men and women, with the possible exception of endocarditis.

Based on an evaluation of valve-related adverse events following MVR for patients in the Medtronic Long-Term Clinical Study and patients in the Toronto Case Series, the freedom from valve-related adverse event rates were similar for men and women, except for valve-related death. In the Medtronic Long-Term Clinical Study, freedom from valve-related death was similar for men and women. However, in the Toronto Case Series, freedom from valve-related death was higher for men than for women. Therefore, the results for valve-related adverse events following MVR presented in the analyses are representative for both men and women, with the possible exception of valve-related death.

Based on an evaluation of mean gradient, effective orifice area, and valvular regurgitation, hemodynamic performance of the aortic and mitral Hancock II bioprostheses was similar in men and women. Therefore, the hemodynamic results for these parameters presented in the analyses are representative for both men and women.

11. Risk - Benefit Analysis

Laboratory and clinical data provide reasonable assurance that the Medtronic Hancock II Bioprosthetic Heart Valve is safe and effective when used according to the approved labeling.

12. Conclusions Drawn from Studies

The laboratory and engineering studies performed on the Medtronic Hancock II Bioprosthetic Heart Valve demonstrate that the device design is safe and effective for human clinical use.

The laboratory testing performed on the device suggests that this device is suitable for long-term implant. The Medtronic Hancock II Bioprosthetic Heart Valve meets acceptable performance specifications.

The animal studies show that the Medtronic Hancock II Bioprosthetic Heart Valve is safe for valve replacement

The clinical studies submitted in the PMA provide sound scientific evidence that the Medtronic Hancock II Bioprosthetic Heart Valve is safe and effective for use as a replacement of an impaired aortic or mitral native or prosthetic valve.

13. Panel Recommendations

On June 24, 1999, the Circulatory System Devices Panel reviewed the data submitted by Medtronic Heart Valves in support of marketing approval for the Medtronic Hancock II Bioprosthetic Heart Valve for use as a replacement of an impaired native or prosthetic heart valve.

The panel recommended that the device be approved without conditions, and recommended some modifications to the labeling.

14. FDA Decision

FDA agreed with the decision of the Panel, and worked with the firm until all labeling issues were satisfactorily addressed. FDA also completed the review of an amendment to the file relating to issues regarding the engineering tests performed on the valve. FDA issued an approval order on September 28, 1999. The firm was in compliance with GMPs.

15. Approval Specifications

Direction for use: See Final Draft Labeling (Information for Use).

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings and Precautions, and Adverse Events in the Final Draft Labeling. Information for Use)

Post-approval Requirements and Restrictions: See Approval Order.