SUMMARY OF SAFETY AND PROBABLE BENEFIT

1. General Information

Device Generic Name:	Implantable Replacement Heart
Device Trade Name:	AbioCor® Replacement Heart
Applicant's Name and Address	ABIOMED, Inc. 22 Cherry Hill Drive Danvers, MA 01923
Humanitarian Device Exemption Number:	H040006
Date of Panel Recommendation:	June 23, 2005
Date of Good Manufacturing Practices Inspection:	January 12, 2004
Date of Notice to Applicant:	September 5, 2006

2. Indications for Use

The AbioCor® is indicated for use in severe biventricular end stage heart disease patients who are not cardiac transplant candidates and who

- are less than 75 years old,
- require multiple inotropic support,
- are not treatable by LVAD destination therapy, and
- are not weanable from biventricular support if on such support.

3. Contraindications

Contraindications include:

- Presence of other irreversible end organ dysfunction that would compromise survival
- Inadequate psychosocial support
- Preoperative noninvasive anatomical assessment indicating inadequate fit (i.e. thoracic volume is unable to accommodate the device)
- Presence of coagulation disorders

4. Warnings and Precautions

General:

- The anticoagulation status of the patient should be closely monitored.
- Do not enter areas or rooms with signs indicating magnetic resonance imaging (MRI) or high magnetic field environment
- Do not place TET (Transcutaneous Energy Transmission) near metal elements
- Internal low battery alarm requires immediate TET attachment
- Low flow alarm requires clinical attention (call the hospital VAD coordinator within 5 minutes of the alarm)
- TET decoupling alarm requires need to check TET coupling within 5 minutes
- Cardiopulmonary Resuscitation (CPR) should not be administered on AbioCor® patients
- Air travel is restricted to overall 2,500 ft altitude change. Specifically, emergency helicopter transport should stay below this limit.

Warnings associated with potential adverse events:

- Strokes may occur that could result in incapacitation and death
- Device may stop suddenly leading to death
- Bleeding (hemorrhage) and thrombosis (clotting) may occur that require additional surgery or procedures
- Surgery is required if the internal battery or TET needs replacement
- Infection may be a complication mostly during the recovery period in the hospital
- Kidney, liver, and lung complications may occur that require treatment
- Recovery may be extended in duration and may lead to depression and other psychiatric disorders

5. Device Description

The AbioCor® is a pulsatile electrohydraulic implantable replacement heart capable of delivering up to 8 L/min pump output over a broad range of physiologic pressures. System control is achieved on a beat-by-beat basis targeting a constant stroke volume to insure repeated full filling and full ejection.

Except for the inflow cuffs and the outflow graft connectors, which are constructed from standard medical grade velour patches and grafts, the blood contacting components of the AbioCor® are made from Angioflex®, a polyether-urethane. Titanium is used as the casing material to avoid corrosion. Medical grade epoxy is used to provide rigidity to nonmoving portions of the blood pumps. The flow paths through the pumps are designed to avoid creation of regions of stasis. The inflow and outflow valves are designed to maintain proper washout of the leaflets.

The hydraulic system that powers the device consists of a miniature centrifugal pump and a reciprocating switching valve which reverses the direction of the fluid flow on every beat. The hydraulic fluid actuating the flexing membranes, which keeps the hydraulic fluid separate from the blood, simultaneously results in the filling of blood on one side while ejecting blood on the other side. Systole on the left side occurs synchronously with diastole on the right side and vice versa.

The AbioCor® can accommodate the difference in cardiac outputs required between the left and right ventricles. In the normal anatomy, physiologic shunts exist which allow higher left side cardiac outputs compared to the right side. In the AbioCor®, a hydraulic balance chamber (See Figure 1) is used to shunt the right chamber volume (also known as shunt flow), thus reducing the right side cardiac output relative to the left side. This feature allows the maintenance of physiologic left atrial pressure.

Implantation of the AbioCor® is achieved while on cardiopulmonary bypass (CPB). The diseased ventricles are excised and cuffs are sewn to the two atrial remnants. Aortic and pulmonary grafts are sewn in place. The cuffs and grafts have mating connectors to the inflow and outflow ports of the device facilitating a snap on coupling. De-airing must occur before the transition from CPB to the AbioCor®.

The system can be divided into 3 subsystems: the Implantable Replacement Heart Subsystem, the External Console, and the Patient Carried Electronics (PCE) Subsystems. The general description of their respective functions follows.

5.1 The Implantable Subsystem

The Implantable Subsystem consists of all of the components that are required to be implanted for normal operation of the AbioCor®. The main components of this subsystem are described below. Figure 1 shows the anatomical placements of these components.

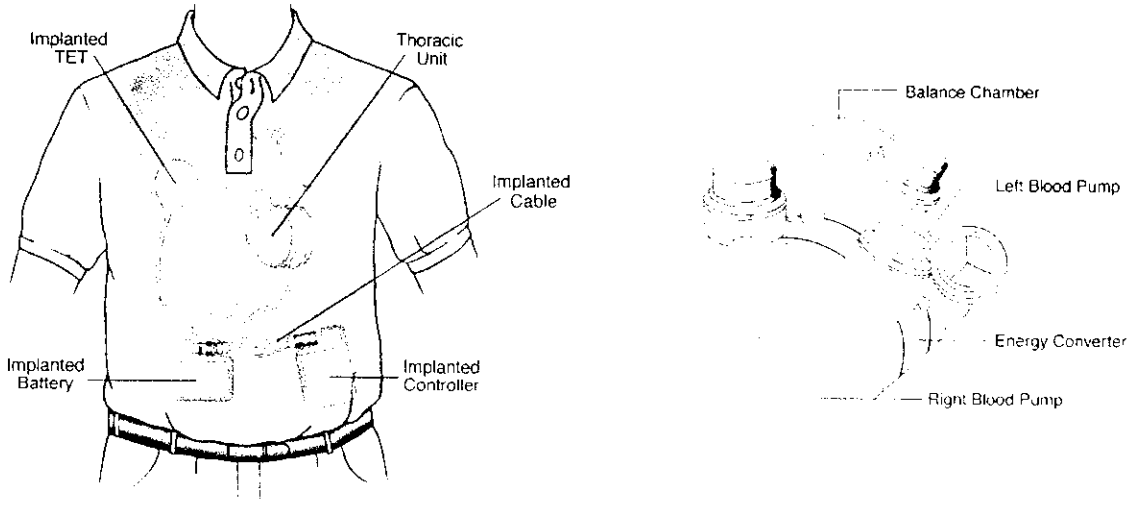

Figure 1. Implanted components

5.1.1 Thoracic Unit (TU)

The Thoracic Unit (TU) converts electrical power into blood motion to support the circulatory system of the patient. The TU is implanted in the space vacated after excising the native ventricles. The TU alternately ejects blood into the systemic and pulmonary circulations.

5.1.2 Implantable Controller

The Implantable Controller is the "brain" of the entire system. It is microprocessor based and provides control and monitoring of the TU. It also has the capability to receive and transmit information to the external systems via a radio frequency (RF) communication link.

5.1.3 Implantable Battery

The Implantable Battery is a rechargeable, lithium ion-based power source that can maintain normal operation of the implantable system in the absence of an external power source for approximately 60 minutes.

5.1.4 Implantable Transcutaneous Energy Transmission Coil (iTET)

The Implantable Transcutaneous Energy Transmission Coil (iTET) receives power inductively from an external power source and converts it into direct current (DC) to power the implantable subsystem.

5.1.5 Implantable Cable

The Implantable Cable connects the various components of the Implantable Subsystem together. The cable also has an integral antenna that is used for the RF communications.

5.2 External Subsystem

The External Subsystem consists of all of the components that are required to support normal operation of the AbioCor® for implantation, ICU recovery, patient ambulation, and out-of hospital use. The main components of this subsystem are described below. Figure 2 illustrates external components and their functional relationship with the implanted system.

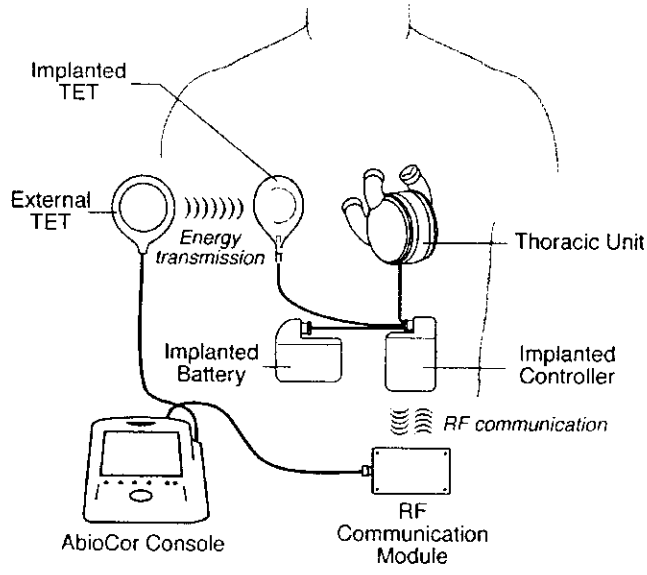

Figure 2. External components and their functional relationship with the implanted parts

5.2.1 Console

The Console allows monitoring primarily of the Implantable Subsystem parameters and alarms as well as the ability to make changes in system run conditions. There are several modes of access designed for safe system operation. For instance, the console can stop operation of the TU only during implantation. This function, essential during intraoperative de-airing of the TU, is not accessible in any other functional mode. In the home screen mode, the display is significantly simplified to avoid information overload or potentially harmful actions by the user.

The Console also has drive circuitry to power the External Transcutaneous Energy Transmission Coil (eTET).

5.2.1.1 External Transcutaneous Energy Transmission Coil (eTET)

The eTET allows delivery of electromagnetic energy to the iTET. There are two different eTET cable lengths to accommodate various use environments. A Duoderm based Velcro patch is used to anchor the eTET at the skin region overlying the iTET.

5.2.1.2 Radio Frequency Communications Assembly (RF Comm)

The Radio Frequency Communications Assembly (RF Comm) gives the console the wireless communication bi-directionally between the external and the Implantable Subsystems.

5.2.2 Patient Carried Electronics (PCE) Subsystem

The Patient Carried Electronics (PCE) Subsystem consists of all of the components that are required to support normal operation of the AbioCor® for periods of full patient ambulation in different environments, for example, in hospitals, restaurants, office buildings, vehicles, homes and outdoors. It supplies power to the internal system via the eTET. The main components of this subsystem are described below. Figure 3 shows the PCE system:

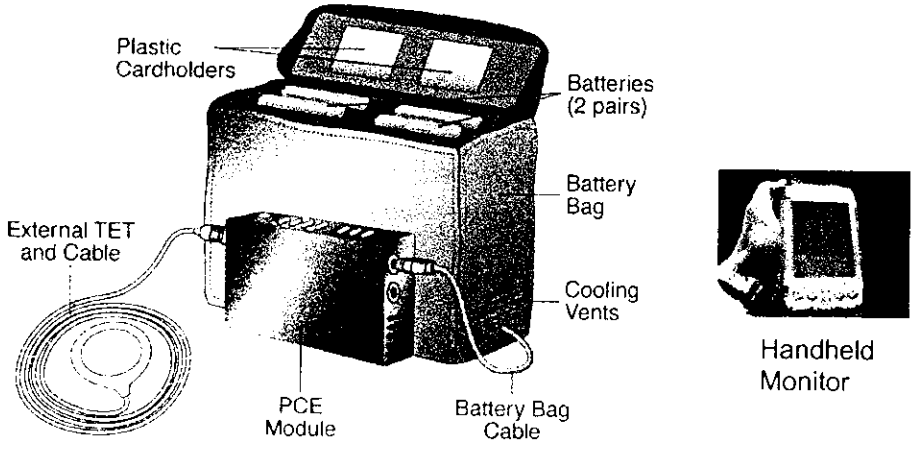

Figure 3. The PCE system and Handheld Monitor

5.2.2.1 PCE TET Driver

The lightweight PCE TET Driver has the circuitries to drive the eTET and to enunciate simple alarms such as low battery, eTET decoupling, excess PCE temperature, and a general Implantable Subsystem alarm.

5.2.2.2 External Transcutaneous Energy Transmission (eTET) Coil

The PCE uses the same eTET coils that are used for the external console.

5.2.2.3 PCE Power and Bag

The PCE Batteries are the primary power source for the PCE TET Driver (PCE Module). The PCE Batteries are discharged in pairs. Two sets of batteries are provided to allow for appropriate backup. The battery sets and the eTET are housed in a PCE bag specifically designed for portability.

5.2.3 Handheld Alarm Monitor

The Handheld Alarm Monitor (Figure 3) allows the user to find out specific details regarding Implantable Subsystem alarms and operation that are enunciated on the PCE TET Driver. This device allows clearing of the alarm when the condition has resolved. This unit relieves the patient from needing to be near the console

to have full diagnostic capability. This unit does not provide control of the internal system, that function requires the console.

5.2.4 PCE Alternating Current (AC) Converter

The PCE AC Converter is an alternate power source for the PCE TET Driver. It permits a patient while stationary to be able to use the PCE TET Driver for an unrestricted amount of time without the need to actively manage PCE Batteries.

5.2.5 PCE Battery Charger

The PCE Battery Charger is a 10-bay charger that allows the patient to charge up to 5 sets of PCE Batteries. It also provides diagnostic information on the state of charge of the PCE Batteries.

5.3 Implantation Accessories

Accessories to facilitate implantation include specially designed wrenches to tighten or loosen electrical connectors between implantable components, tools to connect the device to the atrial cuffs and arterial grafts, instruments to check the integrity of anastomoses, dummy models of electronic packs for pocket sizing, and dummy thoracic unit for sizing graft lengths needed for the anastomoses.

5.4 Safety Elements

Many safety elements are incorporated into the AbioCor® system including:

- Clinical and technical support 24 hours a day, 7 days a week
- Complete backup system in each hospital implanting the device
- Backup external Patient Carried Electronics for home use
- Multiple alarm paths for low internal battery, low flow conditions
- TET self shut down under overload condition(s)
- No skin penetration for external power transfer
- Internal battery capacity of approximately 60 minutes
- Continuous monitoring of the implantable system

6. Alternative Practices and Procedures

There are no other devices on the market that address the same patient population as the AbioCor® because AbioCor® candidates are in biventricular failure and are not cardiac transplantation candidates. Patients may receive palliative care at home, at a hospice, or optimal medical management in the hospital.

7. Marketing History

The AbioCor® has never been marketed in or outside the United States.

8. Potential Adverse Events

Based on clinical experience, the following adverse events can potentially occur in patients implanted with the AbioCor®:

- Death
- Stroke
- Bleeding
- Reoperation
- Hemolysis
- Infection (all causes)
- Renal dysfunction
- Hepatic dysfunction
- Respiratory dysfunction
- Neurologic dysfunction
- Thromboembolism
- Mechanical failure
- Electrical failure
- Psychiatric event

9. Summary of Preclinical Studies

Preclinical testing consisted of bench testing and animal testing.

9.1 Bench Testing

Bench testing consisted of performance, safety, and reliability testing.

9.1.1 In Vitro Testing

In vitro performance testing consisted of the thoracic unit, TET, and battery characterization. Table 1 shows a summary of test description and acceptance criteria. All systems must meet the performance criteria to be accepted for use.

Tests	Description	Test Range	Acceptance
Flow	Test is performed with the thoracic unit in a 37 °C in vitro loop. AoP, PAP, and RAP can be independently set. Left-right flow difference is tested by adjusting the shunt flow.	AoP : 60 – 140 mmHg PAP : 10 – 90 mmHg CVP : 5 – 20 mmHg Beat Rate: 80 – 170 BPM Shunt flow from fully closed to fully open	LAP: 3 – 25 mmHg Stroke Volume : 45 – 60 cc Left-right flow difference is within 0 to 10% of the cardiac output
TET	The power delivery capability of the TET system is determined by varying the axial separation and the radial displacement of the external coil relative to the implanted coil. The delivered voltage to the implanted electronics must be within range over a power load range.	Implantable system power load: 10 – 40 watts TET separation Axial: 0 – 0.7 in Radial: 0 – 1 in	Internal system voltage: 28-32 volts
Internal Battery	Under a constant load, discharge time is measured	Internal load – 20 watts	Discharge time from fully charged at 25 V to a discharged voltage of 19.5 V must be ≥ 60 minutes
PCE Battery	Under a constant load, discharge time is measured	40 watts TET at 0.5" separation	Discharge time from fully charged at 24 V to a discharged voltage of 19 V must be ≥ 60 minutes

Table 1. In vitro testing

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Performance testing was conducted over a physiologic range for AoP (aortic pressure), PAP (pulmonary artery pressure), and RAP (right atrial pressure) and beat rates shown in Table 1, and a shunt flow (left minus right flow) of 0 to 10 % of cardiac output. Within these ranges, the system is capable of providing 4 to 8 L/min of pump output. The TET system is capable of supporting system operation with radial displacements and/or axial separations of better than ± 0.5". The internal battery is capable of supporting a 60 minute untethered operational at a pump output of 6 L/min and 100 mmHg systemic afterload. The external Patient Carried Electronics can provide 60 minutes of operation from one set of batteries. The internal-external RF communication module functions to provide alarms and inputs to the internal system. All input requirements were tested and verified.

9.1.2 Safety Testing

A broad spectrum of safety testing was conducted. Standard test protocols and acceptance criteria established for medical device testing are referenced for each test. The AbioCor® passed all of the standard safety tests.

9.1.2.1 Electromagnetic Compatibility

The AbioCor® system passed all Electromagnetic Interference and Electromagnetic Compatibility requirements based on FCC CFR 47 Parts 15 and 18, CISPR11, and IEC 60601-1-2 for intentional and unintentional radiators. The test for radiated emission ranged from 150 KHz to 1GHz. Conducted emission was tested from 150 KHz to 30 MHz.

9.1.2.2 Biocompatibility

All implanted components of the AbioCor® were tested for biocompatibility to EN ISO 10993-1:1997. Tests included cytotoxicity, sensitization, irritation, pyrogenicity, genotoxicity, subchronic, and chronic toxicity (3 month test duration). All tests passed the respective test acceptance criteria.

9.1.2.3 Sterility

The Implanted Components are ETO sterilized. The process was verified according to ANSI/AAMI/ISO 11135-1994. A sterility assurance level of 10^{-6} was demonstrated. ETO residual level was acceptable following 8 days of outgassing. Sterility shelf life has been verified for 15 months.

9.1.2.4 Electrical and Mechanical Safety

Immunity to shock was tested according to NTIS/ECRI PB296-892 and vibration according to RTCA/DO-160C. Packaging integrity for various parts

was tested to ISTA 3C. Components were subjected to fluid ingress testing (EN 60529). The AbioCor® system satisfied additional electrical and mechanical safety requirements of UL 2601, including cable flexing and pull tests, and electrical insulation integrity tests.

9.1.3 Reliability

Twenty-five implantable subsystems were placed on reliability testing. The test loop was maintained at 37 °C with implanted components immersed in a normal saline environment and pH buffered to 7.4± 0.2. Failure times ranged between 8.0 to 57.0 months. The average runtime time was 21.6 months (± 14.1). System reliability is determined to be greater than 80% at a confidence level of 80% for a one-year operation. Three major failure modes were observed: bearing, membrane wear, and fluid ingress. Two of the three failure modes have been observed clinically, a bearing failure at 5 months and a membrane wear at 17 months. Fluid ingress due to a breach of system hermiticity has not been encountered. A needle puncture of a cable sheath was encountered and the cable was surgically exchanged without patient compromise. Modifications have been implemented to reduce membrane wear rate. Similarly, conditions that can accelerate bearing failure have been identified and can be avoided.

Backup consoles and implantable system elements are required in the hospital environment and backup PCEs and Handheld Monitors are required for discharged patients.

9.2 Animal Testing

The objective of the animal studies was to demonstrate acceptable hemocompatibility of the AbioCor® in the calf model prior to the start of clinical trial. The protocol consisted of performing a minimum of five calf implants for the duration of 30-days under GLP (Good Laboratory Practice) in calves weighing from 90 to 120 Kg. The primary endpoints were the elective termination of the studies with freedom from thromboembolic complications and Transcutaneous Energy Transmission device (TET) induced tissue damage during the course of the implant. The results of the animal studies are summarized below.

Fourteen calves completed the 30-day implant study duration. Terminations were elective. The implant courses of these studies were uncomplicated. The results of the studies indicated that after the one-month implants, blood pumps and end organs were generally clean without evidence of thromboembolic problems. Based on the animal studies, no thermal injury problems were anticipated in the operation of the Transcutaneous Energy Transmission system (TET) in humans, and none were encountered.

10. Summary of Clinical Study

The goal of this trial was to assess the safety and probable benefit of the fully implantable AbioCor® replacement heart as a potential therapy for those cardiac patients whose therapeutic options have been exhausted. Implantation of up to fifteen subjects was approved for this trial with the condition that continuation beyond the first and second group of five patients was contingent on at least one patient in each group surviving to 60 days without significant complications.

10.1 Objectives

For those subjects implanted with the AbioCor®, the initial evaluation of safety and probable benefit was to be assessed at 60 days post-implantation. The study would be considered successful if AbioCor® support extended life to 60 days without unacceptable complications, adverse event rates, or quality of life (QOL) deficits in five implanted patients.

10.2 Methods

Candidate selection proceeded in two stages, a screening stage and an implant consent stage. During the screening stage, a comprehensive medical assessment was performed. This assessment included determining the severity of a candidate's heart failure and the potential fit of the device in the patient's thoracic cavity.

Candidates eligible for the trial were those who were not eligible for heart transplantation based on the center's criteria at the time of screening, were in biventricular failure not treatable with implantable LVAD, and were under optimal medical management yet; the clinical judgment of the treating physicians was that patients were unlikely to survive for a month. Patients with irreversible end-organ failure or inadequate psychosocial support were excluded from the trial.

Candidates were excluded if the prognosis for survival was greater than 30% within the next 30 days. The prognosis of survival was based on a clinical judgment of a combination of factors including hemodynamic status, cardiac conditions and end organ status.

To assess the potential for anatomic fit, MRI or CT scans from candidates were used to reconstruct the internal chest dimensions and the anatomy of the patient. A virtual surgery was performed to remove the ventricles and place the AbioCor® in the vacated space. Three critical observations were made to insure fit. The AbioCor® device had to remain within the rib cage, while not interfering with the left bronchus and the left pulmonary veins.

If a candidate passed all the established criteria, a patient advocate would be available to participate in the informed consent process if desired. Although

direct patient consent was preferred, in cases where this was not practical, a legally authorized representative consented on the subject's behalf.

10.3 Description of Enrolled Subjects

Fourteen subjects were enrolled in the trial at 4 centers. Twelve of the 14 subjects were enrolled at 2 centers. All candidates were males due primarily to fit constraints. Table 2 provides a summary of subject demographics. The mean age of this initial cohort was 67 ± 7.9 years, ranging between 51 and 79 years old. The percentage of subjects excluded from transplant due to age was 43% (6/14), to irreversible pulmonary hypertension was 29% (4/14), to malignancy was 14% (2/14), and to multiple comorbidities including diabetes, neuropathy, renal dysfunction, and hepatic dysfunction, was 14% (2/14). The Body Surface Area (BSA), body weights, and heights are also given in the table.

	Average	Stdev	Min	Max
Age (years)	67	7.9	51	79
BSA (M^2)	1.97	0.15	1.72	2.24
Height (cm)	180.	6.2	170.2	189
Weight (kg)	78.1	10.9	60.8	96.3

Table 2. Subject Demographics (n=14)

The preoperative cardiac conditions and comorbidities of subjects are summarized in Table 3. All subjects were in New York Heart Association (NYHA) Class IV heart failure primarily of ischemic origin (12/14) with two being idiopathic. All subjects were bed bound. A majority of the subjects had prior cardiac operations, pacer or Automatic Implantable Cardioverter Defibrillator (AICD) implanted, and/or required Intra-Aortic Balloon Pump (IABP) support. Pulmonary hypertension and renal dysfunction were the two primary comorbidities. Ten of the fourteen candidates required IABP support.

Pre-implant Cardiac Condition or Comorbidity	# of Subjects with Condition (n=14)
NYHA Class IV	14
Re-op	10
Pacer/AICD	10
IABP	10
Ventilator Support	4
Pulmonary Hypertension	8
Renal Dysfunction	9
Liver Dysfunction	4
Diabetes	6

Table 3. Pre-Operative Conditions

Pre-operative hemodynamics are summarized in Table 4. All data were collected within two weeks of implantation. The data in the table represent the average across subjects of a single time point measurement pre-operatively. These averages may not fully reflect subjects' hemodynamics as illustrated by the central venous pressure. The central venous pressure (CVP = average 11 mmHg) spanned a broad range reflecting patients being actively volume managed by infusion, diuresis, and vasoactive drugs. The wedge pressure was elevated (LAP = average 19.9 mmHg).

Mean systemic pressure was 75 ± 9 mmHg. The mean cardiac index was 2.1 ± 0.5 L/min•M^2 under such maximal inotropic support concurrent with counterpulsation support. High levels of inotropic support averaging 2.5 ± 1.0 drug types were needed to maintain marginal cardiac output and systemic pressure.

		Average	Stdev	N
PAP	(mmHg)	34	6.6	14
AoP	(mmHg)	74	6	14
CVP	(mmHg)	11	6.4	14
PCWP	(mmHg)	19.9	5.5	14
Cardiac Index	(L/min-M^2)	2.1	0.5	14
Cardiac Output	(L/min)	4.3	1.2	14
Ejection Fraction	(%)	18.6	3.5	14
PVR	(dynes-sec/cm^5)	305	107	12
SVR	(dynes-sec/cm^5)	1231	349	14

Table 4. Pre-operative Hemodynamics

The systemic vascular resistance (SVR) was 1231 dyne•sec/cm^5 spanning a broader range than normal indicative of both hypotensive and hypertensive conditions of multiple etiologies. The pulmonary vascular resistance (PVR) was elevated at 305 dyne•sec/cm^5.

Table 5 shows the mean dosages for the inotropes used. The dosages were in the medium to high range.

Inotrope	Mean Dosage	Standard Deviation	Number of Patients
Dobutamine - (µg/kg/min)	7.89	4.08	8
Dopamine - (µg/kg/min)	9.16	10.53	6
Milrinone - (µg/kg/min)	0.43	0.24	12
Epinephrine - (µg/min)	3.3	--	1
Norepinephrine - (µg/min)	9.11	--	1
Digoxin - (mg/day)	0.14	0.05	7

Table 5. Pre-operative Inotrope Dosages (n=14)

Pre-operative blood chemistry is summarized in Table 6. The albumin and sodium were low but creatinine and total bilirubin were elevated.

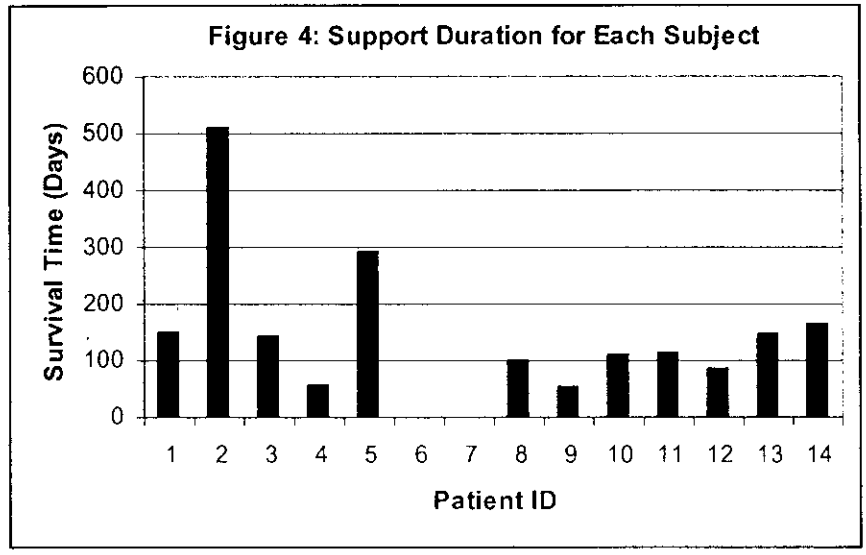
		Average	Stdev	Min	Max	N
Na	(mEq/L)	131.7	6.4	120	141	14
Albumin	(g/dl)	2.8	0.7	2	3.9	11
Creat	(mg/dl)	1.7	0.7	1	3	14
BUN	(mg/dl)	45.1	30.2	16	110	14
T bil	(mg/dl)	1.7	1.8	0.5	7.4	14
ALT	(mg/dl)	63.5	100.2	3	333	14
AST	(mg/dl)	73.1	125.8	10	491	14
Glucose	(mg/dl)	116.7	39.5	59	186	14

Table 6. Pre-operative Blood Chemistry

All subjects entered into the trial met the inclusion criterion of biventricular failure as the basis for exclusion from potential implantable LVAD support. In addition, candidates were excluded if the prognosis for survival was greater than 30% within the next 30 days. The inotrope requirements of AbioCor® subjects averaged 2.5 inotropes.

10.4 Results

Twelve of the fourteen subjects were implanted with the AbioCor® at two centers, with one subject being implanted at each of the other two centers. Twelve subjects survived the implant surgery while two did not. All four centers were successful in their first implant. The twelve subjects were supported by the AbioCor® for a cumulative support duration of 5.2 years. The mean individual survival time for all fourteen subjects was 4.5 months, ranging from 0 to 512 days. The median was 3.6 months. Figure 4 shows the support duration for each subject.



10.4.1 Adverse Events

Recovery was a lengthy process for these subjects. Table 7 lists the major adverse event types experienced by the subjects. Event rates are given in reported incidents per subject per month. The Transient Ischemic Attack (TIA) category includes events that resolved within 24 hours. There were many surgical bleeding events, such as tamponade, occurring during the first few weeks post operatively. The most common events were bleeding and infection unrelated to the device, and respiratory complications. These were followed by neurologic, renal, and hepatic complications.

Event Type	# of Subjects Who Suffered Events	Event Rate (per subject•month)	Total # of Events
CVA*	9	0.29	18
TIA*	3	0.05	3
Non-surgical bleeding	9	0.41	26
Surgical bleeding	10	-	42
Sepsis	2	0.03	2
Infection	11	0.52	33

Hepatic	6	0.11	7
Renal	9	0.13	8
Respiratory	11	0.37	24

*Three subjects had both CVA and TIA and are included in both categories.

Table 7. Adverse Event Rate (n=12)

The propensity for bleeding was high for AbioCor® subjects. 10 of 12 subjects could not tolerate the recommended level of anticoagulation (INR>2.5 or PTT>50 sec) more than 60% of the time, and of these 10 subjects, seven could not tolerate more than 80% of the time. Although the infection rate was high, none of the incidents were related to device infection.

There were two septic events associated with the AbioCor ® subjects, one as a sequella to a massive abdominal bleeding episode. This episode was caused by a femoral vein puncture during a dialysis catheter exchange. The second event occurred in a subject whose suture line did not heal following surgery.

In six subjects, CVA was the cause that led directly or indirectly to the withdrawal of support. The time from CVA to support withdrawal was typically a small fraction of the total support time. The mean time between the terminal CVA event and the withdrawal of support was 17.3 days. Figure 5 shows the total duration of support for these six subjects and the time between the CVA event and the withdrawal of support (shown as solid part of the bar). This latter time span was governed either by signs of recovery based on medical reasons which later reversed course or by family members.

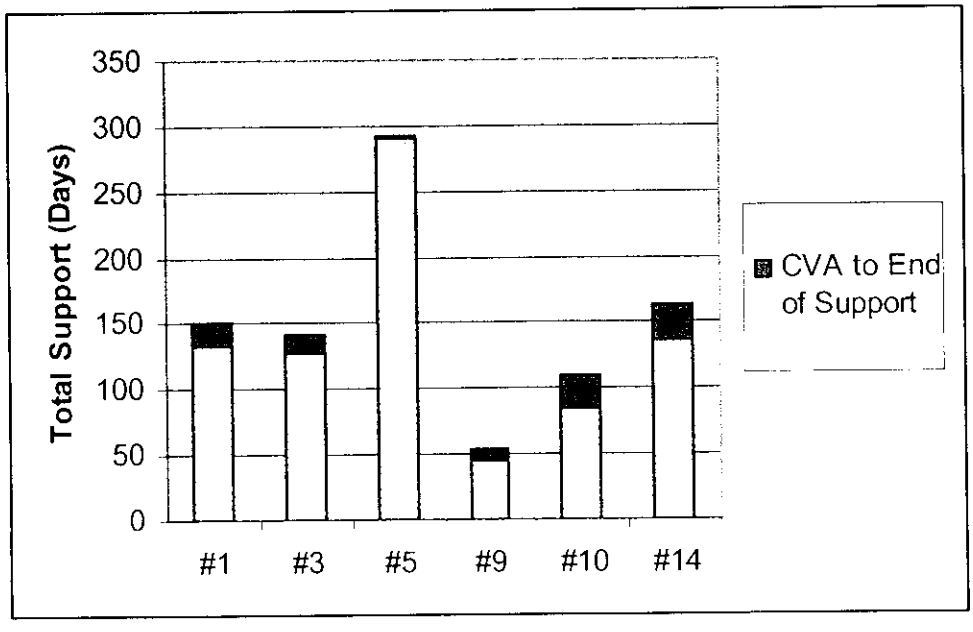


Figure 5. Support Time and CVA to End of Support

Two factors contributed to the CVAs. Tissue contact with the inflow structure was the most likely cause of thrombus formation and subsequent embolic complications despite appropriate levels of anticoagulation and antiplatelet therapy as observed in 3 of the first 5 subjects implanted. Following the identification of the tissue contact problem and the elimination of the tissue contact with the inflow structure, two subjects who were adequately managed with anticoagulation and antiplatelet therapy were free from CVA complications, while all 5 subjects who could not be anticoagulated adequately had CVA events. Adequate therapy was defined as a subject having >20% of the time being on either coumadin or heparin that resulted in INR > 2.5 or PTT > 50 sec, or being dosed with two or more baby aspirin tablets (> 81 mg) or at least one tablet of clopidogrel.

10.4.2 Device Malfunction-Related Adverse Events

There were two device malfunction-related subject deaths. A subject died due to a membrane wearing out at 17 months, an anticipated wear out mode at operating times of around one and one-half years. The subject declined the option for a device replacement. A second subject died due to a motor-bearing stoppage at 4.8 months. The cause was traced to a combination of factors leading to system operation outside of the system design. Corrective actions have been implemented to avoid such future combinations of circumstances.

10.4.3 Outcome

Two patients did not survive the operative procedure. For the remaining twelve AbioCor ® subjects in the trial, all lived out the remaining portions of their lives on the device. Support to six of the twelve subjects was withdrawn secondary to CVAs. There were two device failures. Four subjects died of multi-organ failure or sepsis.

The two operative deaths were due respectively to uncontrollable bleeding and pulmonary embolus caused most likely to the use of factor concentrates following protamine reversal. Three of the six CVA-related deaths were due to inflow structure thrombosis, while the remaining three were due to factors preventing adequate anticoagulation of the subjects. One device failure was due to membrane wear and the other due to motor stoppage. The causes of those subjects who died of multi-organ failure or sepsis were secondary to (1) a vein puncture from a dialysis catheter leading to abdominal bleeding, aspiration, and subsequent sepsis, (2) unhealed suture wound, and (3) two cases of pre-existing hepatic dysfunction that failed to reverse.

10.4.4 Post-operative Clinical Performance

AbioCor® was able to immediately correct cardiac output failure. Figure 6 shows the pump output provided by the AbioCor®. The figure contains data for the twelve supported subjects. The figure includes the preoperative average of each parameter (▪) as the first datum plotted. Daily averages are plotted along with the respective standard deviations. The number of contributing subjects decreased as time progressed. Patient cardiac output increased by 50% on the AbioCor®.

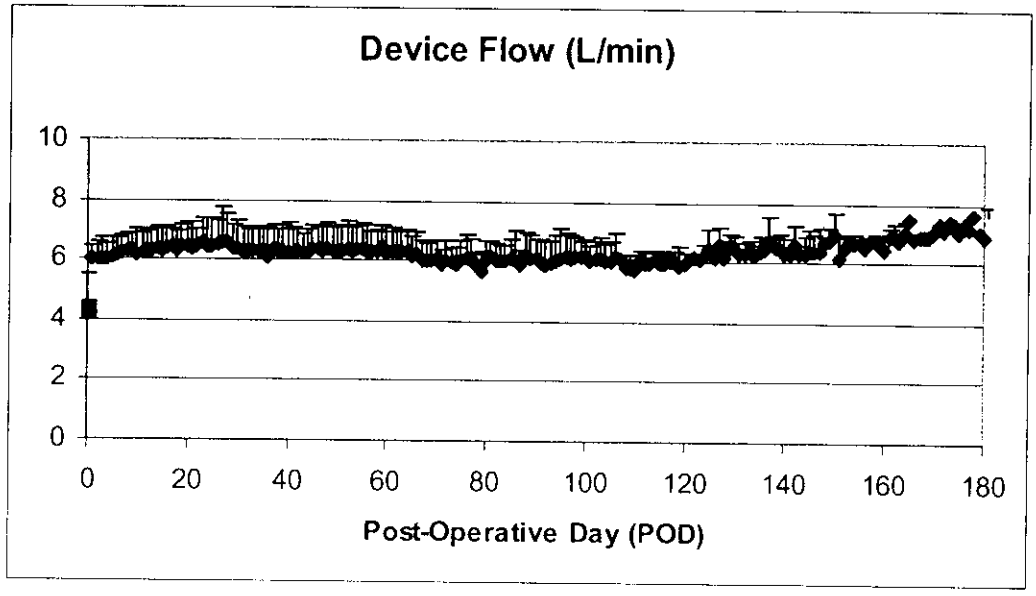


Figure 6. Pump Output

Hemodynamic monitoring was maintained only for a short duration post operatively mainly to avoid complications associated with extended use of indwelling lines. Table 8 shows the means of the pre vs post AoP, LAP, and CVP for the subjects. The increased AoP and the reduction in the LAP were expected on the AbioCor ®. CVP did not decrease.

	Pre-op Mean and Stdv	Post-op Mean and Stdv	p-value
AOP	74 ± 6	86.9 ± 6.4	0.0001
LAP	19.9 ± 5.4	13.6 ± 5.4	0.001
CVP	11 ± 6.4	13.7 ± 2.8	N.S.

Table 8. Physiologic Pressures (mmHg) Across Subjects

In general, over time renal function, as measured by creatinine, improved. Although total serum bilirubin levels increased post-operatively, over a one-month duration of reliable pump output, these values returned to normal.

All subjects experienced bleeding complications. Respiratory complications requiring ventilatory support during some portion of their recovery periods were administered to 11 of the 12 subjects. Eight subjects required dialysis due to renal dysfunction episodes, seven of whom resolved. For one subject, renal support was chronic both pre-operatively and post-operatively. Six subjects had post-operative hepatic failure, three of whom had pre-existing conditions. Support termination for two of these three subjects was related to the hepatic condition. One subject with pre-existing condition recovered from his liver dysfunction. All three subjects without pre-existing conditions recovered from their respective hepatic episodes.

During the trial, the AbioCor ® demonstrated good performance. One subject developed extreme acidosis with pH<7 for a period of ~ 3 hrs during which the AbioCor ® continued to pump while the subject was treated with veno-veno Extra-Corporeal Membrane Oxygenation which reversed the hypoxic condition.

One subject developed malignant hyperthermia (106-107 °F) lasting for approximately 40 hrs. The AbioCor ® continued to perform while the subject's temperature was controlled by the use of dantrolene.

Additionally, the AbioCor ® functioned without compromise during extreme pulmonary hypertension. In at least one case, the Abiocor ® maintained 6-8 L/min of cardiac output despite having to pump against a pulmonary pressure of approximately 60 mmHg.

10.4.5 Quality of Life as Evidence of Probable Benefit

For subjects with no other treatment options, AbioCor ® represents a potential benefit of additional time to live for an end-stage heart failure population.

Two subjects did not survive surgery and two others did not survive beyond 60 days. The ten subjects who survived the initial surgery and lived beyond 60 days experienced varying degrees of benefit. Four of the 10 patients had out-of-hospital activities. The remaining 6 patients attained various levels of recovery including walking, ambulating regularly, and in-hospital excursions. All ten patients implanted with the AbioCor ® were able to interact with family members and were able to give and receive hugs, hold hands, smile and exchange conversation.

The Minnesota Living with Heart Failure (MLWHF) tool was utilized to assess the subjects' quality of life. The MLWHF is based on perceived change relative to pre-implant assessment. Lower scores imply better QOL. However, several

ıbjects were unwilling or unable to complete the questionnaire. Figure 8 ımmarizes the MLWHF data. The pre-implant mean score was 80 ± 12 (n=13), ıile the post-implant mean score was 47 ± 23 (n=9). Typically, New York ɜart Association (NYHA) Class IV patients have MLWHF scores in the 60's, ıile NYHA Class III patients are in the 50's. Seven of nine subjects with pre- ıd post-operative data showed QOL improvement at least one point in time.

order to account for unanswered questions in the MLWHF questionnaire, pre- ıd post-operative questions that were answered were included in the analysis. ɜing this matching analysis, six subjects retained QOL data based on either eir mean post-operative QOL or the last QOL prior to support termination. All ne subjects with post-operative QOL data had at least one QOL measured ɜtween one and three months. For the two subjects that lived beyond 6 onths, the average intervals between QOL assessments were 2.1 months for ıe and 4.7 months for the other subject. For the 7 subjects that lived for less an 6 months, the mean duration between QOL assessments was 1.1 months. ıe interval between the last QOL assessment and termination of support was 1 months with the longest interval being 2.8 months.

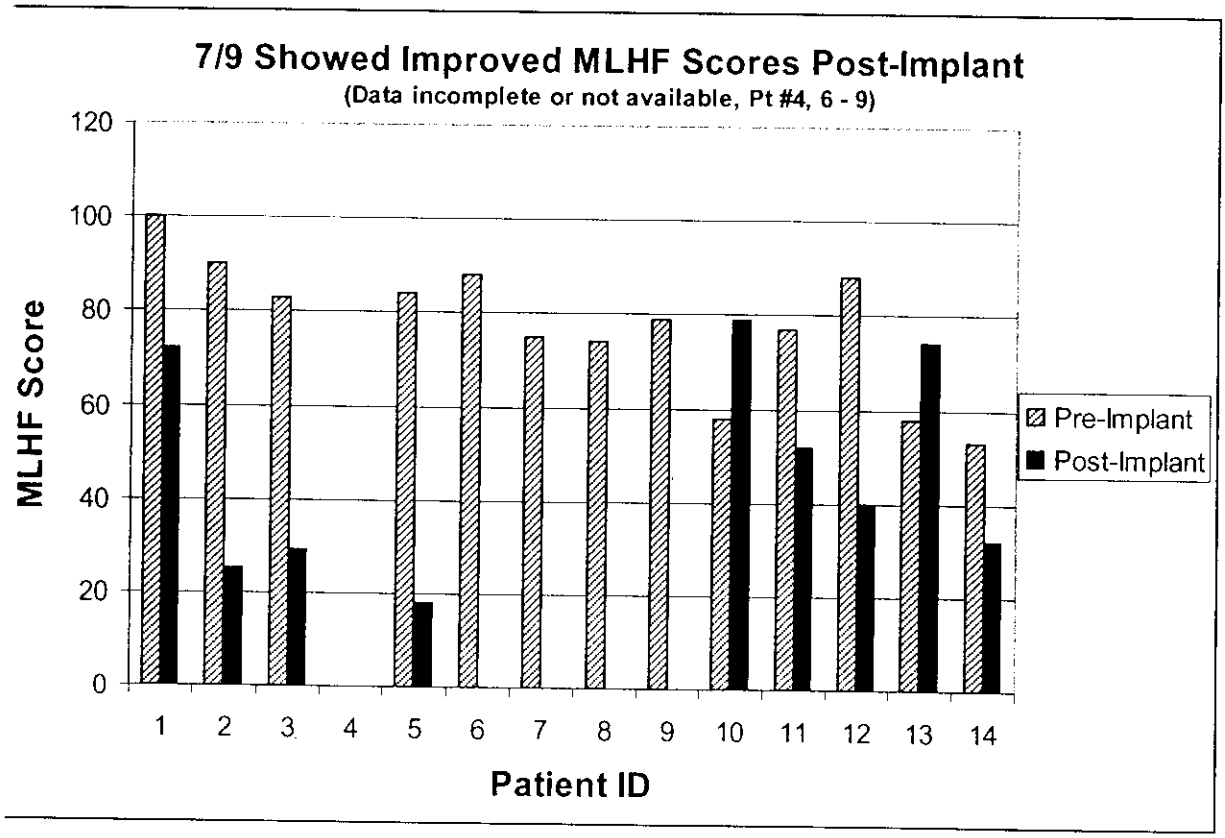


Figure 8. Pre- and post-implant MLHF Scores of AbioCor® subjects

Activity benefit was based on ambulation and in-hospital excursions. Interaction was based on the subject's ability to communicate with family members and friends post-implant.

11. Safety and Probable Benefit

The results of the initial study of the AbioCor® provided the following safety data in subjects with severe end-stage heart failure facing imminent risk of death. Two device failures occurred, one anticipated and one unexpected, representing ~ 83% (10/12) failure-free device operation clinically consistent with the demonstrated one year bench operation. The observed stroke rate was 0.29 per subject-month. No device-related infection problems were observed in AbioCor® subjects. Safety features for power management have been built into the system to avoid unintentional misuses that may result in hazards.

The device restored normal hemodynamics and afforded dysfunctional end organs (e.g. kidney and liver), a chance of recovery. Although only two subjects were discharged from the hospital, one to home and the other to a hotel near the hospital, their experience showed that they and their caregivers managed the system outside of the hospital environment, in their home and community settings.

12. Panel Recommendation

The Circulatory System Devices Panel met on June 23, 2005 to review the data in the HDE application. During the course of voting, a motion to recommend that the HDE application be found Not Approvable failed. However, the final vote of the panel ended in a 7 to 6 (with 1 abstention) vote that the data presented to the panel did not meet the HDE requirements of safety and probable benefit. Subsequent to the final vote, the panel discussed numerous proposals regarding whether to approve the HDE with various conditions of approval. Ultimately, no approval recommendation was made by the panel. The Panel did recommend that the sponsor maintain a Data Registry and form an Anticoagulation Committee to review the anticoagulation protocol and monitor the anticoagulation management of future AbioCor® recipients.

13. CDRH Decision

The regulatory basis for approving an HDE (21 CFR 814.104) is that the device must not pose an unreasonable risk of illness or injury and that probable benefit of the device must outweigh the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

In determining whether these criteria are met for the Abiocor device, FDA considered three primary questions: 1) Is the device able to achieve the necessary level of circulatory support? 2) Is the device sufficiently reliable? 3) Does the device

offer a probable benefit to patients and not pose an unreasonable risk of illness or injury?

The preclinical, animal, and clinical data all demonstrated that the Abiocor device is able to achieve the desired level of cardiac support. Although the clinical study results indicated a concern regarding the long-term reliability of the device, Abiomed has made changes to the device that FDA believes will improve its reliability and durability.

In determining whether the device offers a probable benefit that outweighs the risk of injury, FDA first took into account currently available devices and alternative forms of treatment for this patient population. The Abiocor patient population is one that has already failed to be helped by optimal medical management. Although there is one left ventricular assist device approved for destination therapy, that device is not indicated for non-cardiac transplant eligible patients in biventricular failure. FDA concluded that this is a patient population for whom there are no other treatment options.

FDA also considered the recommendation of the Circulatory System Devices Panel. Although the Panel's final recommendation was that the HDE be found Not Approvable, FDA received additional information from Abiomed following the panel meeting that addresses many of the panel's most significant concerns. In particular, FDA reviewed additional information on anticoagulation, determination of biventricular failure, and neurological assessment and quality of life.

To address the concerns with inadequate anticoagulation, Abiomed has created an anticoagulation committee which has proposed a revised anticoagulation protocol which will be used in the post-approval study.

The panel also had concerns about whether the patients in the clinical trial were truly in bi-ventricular failure, and whether there were accepted standards for defining bi-ventricular failure. The sponsor has subsequently provided additional information about the status of the patients in the clinical trial, as well as a more robust set of factors that will be used to define bi-ventricular failure in the post-approval study.

Abiomed also provided additional information regarding the quality of life and neurological status of the patients in the clinical trial. These additional data highlighted the severity of heart failure and the difficulty of determining what constitutes a "benefit" for AbioCor® patients. The additional quality of life data provided was difficult to interpret due to the missing data and since no validated quality of life assessment tool was used, no definitive recommendation could be made on whether the AbioCor® patients truly experienced adequate or improved quality of life while on the device. Nonetheless, patients and family members did suggest that their quality of life was improved while on the device because they

were able to share "significant life events" with one another prior to death. FDA believes that these results suggest that the device is able to achieve a probable benefit in at least some of the implanted patients.

Therefore, CDRH determined that, based on the data submitted in the HDE application, the ABIOMED AbioCor® Implantable Replacement Heart will not expose patients to an unreasonable risk of illness or injury, and the probable health benefit from using the device outweighs the risk of illness or injury.

Because of the relatively small number of patients that formed the basis for this decision, FDA plans to present the results of the first ten patients from the post-approval study to the Circulatory System Devices Panel. This will allow for any changes to the recommended clinical management of AbioCor® patients to occur.

14. Approval Specifications

Directions for Use: See Final Draft Labeling (Instructions for Use)

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

Post-approval Requirements and Restrictions: See Approval Order