
Panel Date: June 23, 2005
To: File, H040006
From: Eric Chen, Biomedical Engineer
Ref: H040006

Company Name: Abiomed, Inc
Device Name: AbioCor[®] Implantable Replacement Heart

Background

This report presents the Food and Drug Administration (FDA) summary of the clinical and pre-clinical testing review memorandums regarding the Humanitarian Device Exemption (HDE) H040006 for the Abiomed AbioCor Implantable Replacement Heart. The AbioCor is the first fully implantable replacement heart for severe end stage heart failure patients who are less than 75 years old, not transplant candidates at the time of assessment, in biventricular failure not treatable by a destination therapy left ventricular assist device (LVAD), require multiple inotropes for support, or those not weanable from temporary biventricular support, if on such support and not awaiting transplantation. The device is designated as a last resort for a small patient population with a poor prognosis of survival within 30 days.

The Office of Orphan Products Development (OOPD) granted Abiomed's request for a Humanitarian Use Device (HUD) in September 2003. The HUD designation qualified the AbioCor for the treatment of a limited end-stage heart failure population of less than 4000 patients annually. After receiving their HUD designation, Abiomed submitted the HDE application to the Office of Device Evaluation for marketing approval in September 2004.

The FDA review team for this HDE file is as follows:

Lead Reviewer	Eric Chen, M.S.
Clinical	Julie Swain M.D. and Ileana Piña, M.D.
Biocompatibility, Packaging, and Sterilization Engineer	Keith Foy, M.S. Michael Berman, Ph.D. and Jean Rinaldi, M.S.
Bioresearch Monitoring	Donna Headlee
Manufacturing	Vertleen Covington
Human Factors and Patient Labeling	Michael Mendelson and Walter Scott, Ph.D.

HDE Chronology

Information supporting the Abiomed AbioCor Implantable Replacement Heart was submitted under the HDE process (H040006). The following table provides a chronology of formal interactions for this HDE. Additional information such as informal e-mails or telephone interactions and formal meetings with the Sponsor throughout the review process is not outlined here.

<i>HDE Chronology for H040006</i>	
<i>Date</i>	<i>Event</i>
September 2, 2004	HDE received
September 15, 2004	HDE filing letter issued by FDA
September 24, 2004	Manufacturing deficiency letter issued by FDA
October 21, 2004	Amendment 1 received with responses to human factors and patient labeling questions
November 11, 2004	Amendment 2 received with responses to GMP deficiency letter issued September 24, 2004
December 22, 2004	Major deficiency letter #1 issued by FDA
January 21, 2005	Amendment 3 received with responses to major deficiency letter #1
March 7, 2005	Amendment 4 received regarding lessons learned from patients #2 and #13
April 12, 2005	Major deficiency letter #2 issued by FDA
June 23, 2005	Scheduled for review by Circulatory System Devices Panel

Humanitarian Device Exemption (Code of Federal Regulations 814, Subpart H)

A Humanitarian Use Device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. A device manufacturer's research and development costs could exceed its market returns for diseases or conditions affecting small patient populations. The HUD provision of the regulation provides an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting these populations.

To obtain approval for an HUD, a humanitarian device exemption (HDE) application is submitted to FDA. An HDE is similar in both form and content to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA. An HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs 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. Additionally, the applicant must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that they could not otherwise bring the device to market.

An approved HDE authorizes marketing of the HUD. However, an HUD may only be used in facilities that have established a local institutional review board (IRB) to supervise clinical testing of devices and after an IRB has approved the use of the device to treat or diagnose the specific disease. The labeling for an HUD must state that the device is a humanitarian use device and that, although the device is authorized by Federal Law, the effectiveness of the device for the specific indication has not been demonstrated.

Executive Summary

The Abiomed AbioCor Implantable Replacement Heart is the first totally implantable artificial heart to be considered for marketing clearance by the FDA for the long term use in patients with severe biventricular heart failure who are not eligible for cardiac transplantation. The AbioCor is

capable of delivering cardiac outputs of up to 8 L/min at physiologic pressures and extreme conditions, not normally supportable by a failing heart. In January 2001, the FDA approved a limited Feasibility Study of the AbioCor in severe end-stage heart failure patients with a poor prognosis of survival within 30-days. At the time of HDE submission in September 2004, 14 patients have been implanted with the AbioCor over a time period from 2001 to 2004. Twelve patients (86%) survived the perioperative period at four different medical centers. The duration of support for all patients ranged from 0 to 512 days with a mean of 138 days. Due to slow enrollment of patients into the feasibility trial, Abiomed and FDA agreed that a multi-center pivotal trial which would have allowed the collection of further data to support a PMA was not appropriate. After discussions with Abiomed, the HDE marketing process was felt to be the best alternative.

It should be noted that HDE applications are not required to have clinical data to support a device manufacturers claim of reasonable assurance of safety and probably benefit in an intended patient population; however, Abiomed has submitted clinical data from their Feasibility Study with the AbioCor Implantable Replacement Heart.

Device Description

The AbioCor is indicated for use in severe end stage heart disease patients who

- are less than 75 years old,
- are not transplant candidates at the time of assessment,
- require multiple inotropic support,
- are in biventricular failure not treatable by LVAD destination therapy,
- are not weanable from temporary biventricular support if on such support and not awaiting transplantation.

The AbioCor (figure below) is a pulsatile electrohydraulic implantable replacement heart capable of delivering up to 8 L/min 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.

The blood contacting components of the AbioCor are made from Angioflex, a polyetherurethane, except for the inflow cuffs and the outflow graft connectors, which are constructed from standard medical grade velour patches and grafts. 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 regions of stasis. The inflow and outflow valves (polyurethane) 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, separating the fluid from the blood, simultaneously affects the filling of blood on one side while ejecting blood on the other side. Systole on the left side is diastole on the right side and vice versa.



The AbioCor has the ability to accommodate the difference in outputs required between the left and the right ventricles. Physiologic shunts exist which normally require higher left side outputs compared to the right side. In the AbioCor, a hydraulic balance chamber is used to shunt the right chamber volume, on a beat by beat basis, thus reducing the right side output relative to the left side. This feature allows the maintenance of physiologic left

atrial pressure.

Implantation of the AbioCor involves removing the diseased ventricles and the cuffs are sewn to the two atrial remnants (figure above). 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.

The system can be divided into 3 subsystems: the Implantable, the External Console, and the Patient Carried Electronics (PCE) Subsystems.

The Implantable Subsystem:

The Thoracic Unit (TU) converts the electrical power into blood motion. The TU is implanted in the space vacated after excising the native ventricles. The TU alternately ejects blood into the systemic and pulmonary circulation. The Implantable Controller (microprocessor based) 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. 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 more than 30 minutes. The Implantable Transcutaneous Energy Transmission Coil (iTET) receives power inductively from an external power source and converts it into DC to power the implantable subsystem. 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.

The initial design of the AbioCor included a cage as part of the inflow sewing cuff. The first five patients were implanted with this cage. This cage was intended to prevent inflow occlusion by atrial tissue which had been observed during animal testing. However, during the Feasibility Study, autopsy clots were observed at the base of some cage struts thought to be in persistent contact with atrial tissue; clots were not seen on other cage struts thought to not have persistent contact with atrial tissue. It was thought that clots similar to those observed might have been contributory to CVAs observed in some of these patients. Accordingly, the Sponsor proposed (and FDA accepted as a 5-day notice to the IDE application – S008) modifying the inflow cuffs to remove the cage; these cageless cuffs were implanted in the next six patients.

It should be noted that some of these later patients with the cageless cuffs also experienced CVAs. The Sponsor concluded that changes in the surgical procedure to accommodate the

cageless cuffs may have contributed their own problems; as well, it was found that multiple other factors may have contributed to the CVAs observed (in patients with the caged and cageless cuffs). The Sponsor proposed to re-introduce the caged cuffs, with a design modification to prevent persistent contact between the cage struts and atrial tissue. Thus, both caged and cageless cuffs were available, to be used at the discretion of the surgeon. Patients #12 to #14 were implanted with the caged cuffs sewn to atrial tissue avoiding both tissue contact of the cages and atrial wall.

External Subsystem

The Console allows monitoring primarily of the Implantable Subsystem parameters and alarms as well as the ability to make system run condition changes. There are several modes of access some that are only accessed during clinical implant of the device and some that are used during usual and customary use of the device (home screen) as to not overload the user. The Console has drive circuitry to power the External Transcutaneous Energy Transmission Coil (eTET). The eTET allows delivery of energy to the iTET. There are two different eTET cable lengths to accommodate various use environments. The Radiofrequency Communications Assembly (RF Comm) gives the console the wireless capability to communicate bi-directionally with the Implantable Subsystem.

Patient Carried Electronics (PCE) Subsystem

The PCE subsystem consists of all of the components that are required to support normal operation of the AbioCor for periods of patient ambulation. It supplies power to the internal system via the eTET. The PCE TET Driver contains the circuitries to drive the eTET, alarms, eTET decoupling, excess PCE temperature. The PCE batteries (discharged in pairs) are the primary battery source for the PCE TET Driver. The Handheld Alarm Monitor provides specific details regarding the Implantable Subsystem alarms enunciated by the PCE TET Driver. The monitor relieves the patients from needing to be near the console to have full diagnostic capability but does not provide control of the internal system, that function requires the console. The PCE AC Converter is an alternative power source for the PCE TET Driver and allows the patient to be powered by wall power without depleting the PCE Batteries. The PCE Battery Charger allows the patient to charge up to 5 sets of PCE batteries.

Clinical

Alternative Practices and Procedures

The AbioCor is designed to serve a subset of transplant-ineligible, end-stage heart failure patients with biventricular failure not treatable by drugs, pacing devices, or approved cardiac assist devices. There is one approved implantable left ventricular assist device for end-stage heart failure patients who are not transplant eligible. There is one approved implantable temporary total artificial heart for bridge-to-transplantation. The AbioCor is intended for a group of patients currently not served by any approved device.

Feasibility Study

The Feasibility Study provided the initial clinical experience with the AbioCor. There was no prospectively agreed upon statistical analysis plan or control group. The Feasibility Study was intended 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 had been exhausted. The initial evaluation of safety and probable benefit was to be assessed at 60 days

post-implantation. Patients in the Feasibility Study were followed until outcome which provided important data on the reliability of the device along with probable benefit of the device in patients. In addition, adverse events were tracked so that the potential risks of the device would be captured. An IDE Feasibility Study of fifteen (15) patients at six (6) centers was approved in January 2001. Fourteen (14) patients at four (4) institutions subsequently were implanted with the device (two institutions implanted 12 of the 14 devices). These 14 patients form the clinical basis of the HDE submission. Table 1 lists the centers that were included in the Feasibility Study and the number of AbioCor implantations that were performed at each center.

<i>Clinical Investigator Centers</i>	<i>Number of Implantations</i>
University of Louisville Jewish Hospital, Louisville, KY	7
Texas Heart Institute, Houston, TX	5
UCLA School of Medicine, Los Angeles, CA	1
Hahnemann University Hospital, Philadelphia, PA	1
University Medical Center, Tucson, AZ	0
Massachusetts General Hospital, Brigham and Women's Hospital, Boston, MA	0

Since the AbioCor was a complex first-of-its-kind device, the Agency created criteria which the Sponsor had to meet in order to continue implanting the device during the Feasibility Study. One criterion was that the Feasibility Study would be stopped if none of the first 5 patients survived beyond 30 days post implant. Another criterion involved an incremental gate for study continuation in each group of five patients. This incremental gate for study continuation required that at least one out of five patients survived to 60 days without significant complications. By using these criteria, the concept of the Feasibility Study could prevent excess risks to additional patients if none of the first 5 patients survived beyond 30 days post implant or if at least one patient out of a group of five didn't survive to 60 days.

Candidate selection proceeded in two stages, a screening stage and an implant consent stage. During the initial screening stage a basic medical assessment to determine the severity of heart failure and potential fit of the device in the patient's thoracic cavity using a virtual surgery program which placed the AbioCor in the chest using the internal chest dimensions from MRI or CT scans. Candidates were excluded from the Feasibility Study if the prognosis for survival was greater than 30% within the next 30 days. This prognosis of survival was based on a combination of hemodynamic status, cardiac conditions, various laboratory values, and end organ status as assessed by liver function tests and serum creatinine, among others.

The Feasibility Study was intended to be followed by a multi-center Pivotal Study. This Pivotal Study would have included a larger number of patients at more clinical investigational centers and agreed upon data analysis and clinical endpoints. However, due to the slow enrollment of patients in the Feasibility Study, the Sponsor and FDA discussed the possibility of the AbioCor qualifying under the HUD designation. *The HUD designation of a device is that it is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4000 individuals in the United States per year.* Information regarding the HDE regulation is included in Section I of this Panel Package. After receiving their HUD designation, the Sponsor formally submitted the HDE application for marketing approval. Therefore, no formal multi-center

Pivotal Study was established to demonstrate that the AbioCor was safe and effective in the intended patient population.

Feasibility Study

Key Inclusion/Exclusion Criteria (Appendix 2.1, Clinical Summary, Panel Package)

The patient population for the Feasibility Study included those heart failure patients who were on optimal medical therapy and met all of the following:

Inclusion Criteria

- The patient must be greater than over 18 years old at the time of screening.
- The patient must be ineligible for cardiac transplantation at the time of screening.
- The patient must have a high likelihood of dying within the next 30 days as predicted by the AbioScore or the AMI-SHOCK tools.
- The patient must have an AbioFit virtual fit evaluation.
- The patient is in biventricular failure.
- The patient is unweanable from a temporary mechanical circulatory assist device.

Exclusion Criteria

- The etiology of the patient’s heart failure has significant potential for reversibility.
- The patient has an AbioScore or AMI-SHOCK predicted mortality likelihood less than 70% within 30 days at the date of screening.
- The patients with other irreversible end organ function that would compromise survival.
- The patient has inadequate psychosocial support.

Baseline Clinical and Hemodynamic Status and Medical Therapy

3/14 patients were on IABP, one was on dialysis, two were on ventilators, and 10 had previous cardiac surgery. Six patients were ≥ 70 years. Table 2 below lists the baseline clinical and mean hemodynamic status of the 14 patients.

Table 2: Baseline Clinical and Hemodynamic Status									
<i>E.F.</i>	<i>ICM</i>	<i>IABP</i>	<i>PA</i> <i>Mean</i>	<i>CVP</i>	<i>SVR</i>	<i>C.I.</i>	<i>TPG</i>	<i>Creat</i>	<i>Alb</i>
19 %	12	3	34.5 mmHg	11 mmHg	1231 dynes	2.1 l/min/m ²	15	1.74	2.8

Values as mean; n=14; ICM = ischemic cardiomyopathy; PA = pulmonary artery pressure; CVP = central venous pressure; SVR = systemic vascular resistance; C.I. = cardiac index; TPG = transpulmonary gradient; Alb = albumin

Patients were considered inotrope dependent. The mean number of inotropes was 2.5. No other information regarding background medical therapy was provided. In the patients excluded for pulmonary hypertension, no data have been provided concerning attempts to lower pulmonary vascular resistance.

Survival estimation:

The AbioScore was used to estimate survival for the inclusion criteria of greater than 70% estimated mortality in 30 days. The AbioScore contains 27 clinical items (such as renal function, NYHA class, etc.). Adequate validation of this prognostic score for 30-day mortality has not

been provided to the Agency. Although there is no known validated scoring system for prediction of 30-day mortality in the type of patients included in the Feasibility Study, the components of the AbioScore include the items normally used by experienced heart failure physicians to make a qualitative clinical estimate of the 30-day mortality probability.

Control Patients

No prospective control patients were evaluated. The Sponsor uses three methods (AbioScore, AMI-SHOCK index, and REMATCH control patients) to attempt to show that the survival of the device patients is improved over that of similar patients not treated with the AbioCor.

AbioScore: The Sponsor has developed a scoring system from 27 clinical variables chosen from 42 patient records (retrospective and prospective, unknown number of each) gathered from 4 centers. There is no evidence that these patients were similar to the biventricular heart failure patients enrolled in the Feasibility Study. The records were selected simply "...based strictly on ICD-9 codes for heart failure and CPT and NDC codes for inadequate hemodynamics...". The Sponsor also recorded whether the patient was dead or alive at 30 days. These patients were not comparable to the AbioCor patients in that their age ranged from 20 to 79 years (vs AbioCor 51-79), 26% were female (vs none of the AbioCor patients), an unknown number had biventricular failure (vs 100% of the AbioCor), and 38% were on LVAD's for bridge-to-transplant (vs. none of the AbioCor patients).

AMI-SHOCK Index: This trial included patients who had cardiogenic shock secondary to an acute myocardial infarction. No patients in the AbioCor group had cardiogenic shock secondary to acute myocardial infarction, so the comparability of these patients is questionable.

REMATCH: The Sponsor states that the patients implanted with the AbioCor can be compared to the patients in the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) study in order to estimate survival probability for patients on inotropes. Different screening methods, inclusion and exclusion criteria, and patient population make the two groups not comparable. The Sponsor attempts subset analysis of the REMATCH trial. It is important to note that REMATCH had only 61 patients in the medical therapy group and that several patients chose to have medical care withdrawn within one month of being randomized to the control group. Subset analysis is not informative with such a small sample size. The New England Journal of Medicine literature paper (Rose et al., 2001, NEJM 345:1435-43) discussing the REMATCH study can be found at the end of this FDA report.

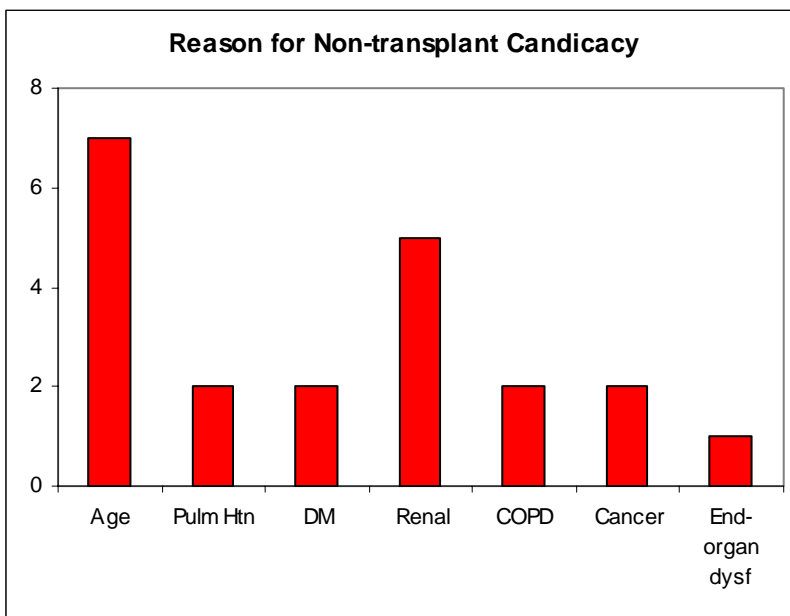
Diagnosis of Biventricular Failure

The Sponsor proposes that the device is intended to be used in patients who are "in biventricular failure not treatable by LVAD destination therapy." The criteria used to determine the inability to tolerate only an LVAD are not provided in the protocol. Review of the literature shows that in the majority of cases, an LVAD is sufficient support for patients with evidence of biventricular failure and highlights how difficult it is to make this assessment *a priori*. It is unclear how RV failure was determined since the average CVP was 11 mmHg.

Reasons for non-transplant eligible:

The primary reason for non transplant eligibility was age (7/14), followed by renal insufficiency in five patients. The baseline creatinine in the five patients diagnosed as renal insufficiency ranged from 1.5 to 3.0. The Sponsor's definition of renal failure as an adverse event is a creatinine of >3.5.

The following graph shows the reasons for transplant exclusion in the 14 patients studied.

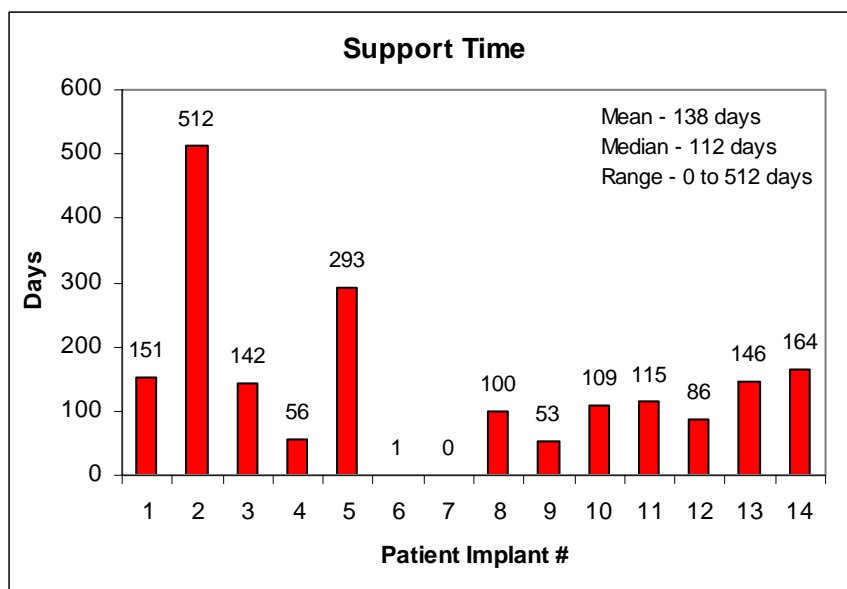


Patient Clinical Course and Followup

Fourteen patients were implanted:

- 2 died during implantation
- 2 additional died before the 60 day endpoint
- 3 of the >60 day survivors had strokes before 60 days
- 1 was discharged home
- 1 was discharged to a hotel

The following graph illustrates the duration of support (until death) of the 14 patients who were implanted with the AbioCor.



For the device to be judged to have probable benefit, ideally both the duration of survival and quality of survival should be improved. The device should prolong functional life. Six patients achieved ambulation and four patients had out-of-hospital excursions. One patient was discharged to home and one to a nearby hotel. However, the information provided by the Sponsor on the potential quality of life (QOL) benefit with the AbioCor device was physician assessed (e.g. first walk, out of hospital excursions, etc.). No patient or family health status (QOL) validated measures were used to evaluate these patients, so the QOL benefit of the device is difficult to determine. Similarly, no physiological assessments of functional capacity (6 min walk, MVO₂) were used. For example, patient #9 lived 53 days on the device. However, the patient never regained consciousness after the implant operation and was kept alive in a comatose state for 53 days until the family requested withdrawal of support. Patients had no formal measures of health status. Therefore, it is difficult to determine the length of life with an acceptable quality of life in this patient cohort.

Safety

The following table 3 shows the length of support and cause of death in the 14 patients as assessed by the FDA from the data provided by the Sponsor:

<i>Pt #</i>	<i>Length of Support (days)</i>	<i>Cause of Death</i>
1	151	Stroke
2	512	Device failure: Device end of life
3	142	Stroke
4	56	Stroke
5	293	Stroke
6	1	Bleeding postop
7	0	Thrombus blocking blood flow intraop
8	100	Multiorgan failure secondary to femoral vein puncture
9	53	Stroke
10	109	Stroke

11	115	Sepsis, multiorgan failure
12	86	Sepsis, multiorgan failure, hepatic failure
13	146	Device failure: Sudden stop of pump
14	164	Stroke

Below is a brief discussion of selected serious adverse events that were experienced by patients during the Feasibility Study. Table 4 below lists the number of patients that experienced selected serious adverse events and the total number of adverse events experienced by the 12 patients who survived implantation of the AbioCor.

Stroke/TIA:

The Agency defines stroke as any neurological event lasting >24 hrs or a patient with a brain imaging study showing infarction. Using this definition, 10/12 patients had a TIA or stroke (4 TIA's and 19 strokes). This analysis differs from the categorization of events by the Sponsor, where the definition of stroke was an event not resolved by 24 hours. For example, Patient #11 was categorized as having a TIA, but the CT scan showed “two new non-hemorrhagic infarcts of the left thalamic region”. Also, there was no evidence of systematic examination of these patients by a neurological expert, so the neurological event rate might have been larger than reported. Difficulties in the management of anticoagulation in these patients might have also had an effect on the number of neurological events that were seen in the Feasibility Study.

Bleeding:

Bleeding was defined as 1) blood loss exceeding 2000 ml in a 12-hour period; (2) bleeding requiring surgical exploration for resolution; (3) collection of clotted blood that requires aspiration or surgical intervention. Similar to stroke/TIA, difficulties in the management of anticoagulation in these patients might have affected the number of bleeding events that were seen in the Feasibility Study.

Infection

Infection was defined as (1) positive cultures of blood, urine, sputum, or surgical wound sites; (2) elevated WBC count (>25,000) or fever 104 degrees F or greater. By this definition, all patients had episodes of infection. In these immunosuppressed, seriously ill patients, the type and rate of infections are not unexpected with mechanical circulatory support.

Renal Failure

Renal failure was defined as (1) a requirement for dialysis or hemoconcentration for more than 3 days, or (2) creatinine greater than 3.5 mg/dL. The incidence of reversible vs. irreversible renal failure cannot be determined from the data presented.

Caged Cuff

The first 5 patients had a cage as part of the atrial sewing cuff, then 6 had implants without the cuff, then 3 patients had caged cuffs with the anastomosis close to the annulus. As mentioned previously, patients implanted with a cage as part of the atrial sewing cuff experienced CVAs, as well as patients with cageless cuffs. Therefore, it is difficult to conclude from the minimal data if the observed CVAs were directly linked to cage or cageless cuffs.

Table 4: Adverse Events Associated with the AbioCor		
<i>Adverse Event</i>	<i># Pts with Event (total 12 pts survived postop)</i>	<i>Total # Events in 12 patients (138 days mean survival)</i>
Stroke	9	19
TIA	3	4
Bleeding/tamponade	12	50
Infection	12	34
Renal Failure	8	8

REVIEW SUMMARY

Non-clinical

For the HDE application, a complete battery of pre-clinical bench testing results was provided for the AbioCor Implantable Replacement Heart. Bench testing consisted of performance, safety, and reliability testing of the device and of the external console.

The reviews of the biocompatibility, electrical safety and electromagnetic compatibility, battery performance, alarms, *in vivo* animal studies, manufacturing, and sterilization information (including packaging and shelf life) have been completed and there are no outstanding issues regarding these parts of the HDE.

The reliability of the device was conducting using twenty-five (25) implantable subsystems with failure times ranging between 8.2 to 40.5 months. The average runtime was 18.8 months. Since the AbioCor cannot be easily replaced and since the device is for permanent implant, system reliability must be of concern. System reliability was determined to be greater than 80% at a confidence level of 80% for a one-year operation. For the external Console and PCE Subsystems, reliability was determined to meet 80% reliability with 80% confidence level for 6 months of operation. Three major failure modes were observed for the AbioCor: bearing, membrane wear, and fluid ingress. Two of the three major failure modes have occurred clinically, a bearing failure at 5 months in Patient #13 and a membrane wear at 17 months in Patient #2.

The device failure (bearing failure) that occurred in Patient #13 involved the AbioCor operating outside of its specified design. Investigation revealed that the actual position of the pump in the patient's chest differed from the position predicted based on pre-placement CT scans; the difference in actual vs. predicted position was greater in this patient than in any of the other patients in this Feasibility Study. In retrospect, the actual position of the AbioCor in the patients' chest predisposed this patient to incidents of low inflow. It was noted that, within a narrow range of left-right flow balance settings, necessary to maintain LAP in a desired range for this patient, the pump intermittently switched between a high and a low value for stroke volume. This behavior, while within specification, was not seen in any other patients. To compensate for this behavior right side flow was reduced, leading to under-filling on the left side. This necessitated an increase in left side filling time, thus reducing left side ejection time. To maintain full ejection the control algorithm for the hydraulic motor increased motor speed, this in turn increased bearing wear. It was this increased bearing wear that ultimately resulted in a premature failure of the hydraulic pump, followed by a (blood) pump stop and patient death. The Sponsor proposed corrective actions for this device failure which the FDA has accepted; therefore, no remaining concerns exist with the bearing failure.

The device failure (membrane wearout) that occurred in Patient #2 was an expected failure mode by the device which had been observed during bench testing. Patient #2 refused to have the AbioCor device replaced when given the option. The Sponsor has tightened the tolerance on the amount of fluid introduced in the energy converter within the current manufacturing specifications in hopes of resolving this membrane wearout mode. However, no data has convincingly demonstrated that the tightening of the tolerance has resolved the membrane wearout mode. The FDA and Sponsor will continue to monitor this membrane wearout mode.

The design change to the caged inflow cuffs to minimize persistent contact between the cage struts and atrial tissue (along with concomitant changes to the surgical procedure) appeared reasonable. Unfortunately, there was no way to convincingly validate the proposed design change on the bench or in animals. Because there was no clear evidence that either the (redesigned) caged or the cageless inflow cuffs were the proximate cause of observed CVAs, and because there was no realistic way to test the redesigned caged cuff, the Sponsor was allowed to offer both caged and cageless inflow cuffs for the remaining patients in the Feasibility Study. At the time of FDA review which allowed the Sponsor to offer both caged and cageless inflow cuffs, only 11 patients had been implanted with the AbioCor leaving the remaining 4 (to be implanted) patients with the choice (cage or cageless) left to the judgment of the surgeon. Since the reintroduction of the caged inflow cuffs, patients #12 through #14 were implanted with caged cuffs.

The draft Summary of Safety and Probable Benefit of the Panel Package includes the summaries of the pre-clinical testing data provided in the HDE.

Clinical

The device was implanted in patients who were in end stage heart failure, were refractory to medical management and who, in the judgment of the investigational sites appeared not to have any other options to prolong survival. The AbioCor has demonstrated that it can support patients by providing physiological cardiac outputs. Several patients had improvement and/or stabilization of renal and hepatic function. Some patients could sit, walk, and take excursions outside of the hospital. However, the expected duration of survival and the expected quality of life is difficult to determine from the limited data set available.

Training

Each center will be qualified for AbioCor implant through a training program similar to that used for sites in the clinical trial. Three sessions consisting of didactic and animal implantation will be undertaken at a training site with animal facility for acute implantation of the AbioCor. The training center will be responsible for IACCU approval for the training studies. A more detailed discussion of training is provided in the Instruction for Use in the Panel Package.

Post-approval Plan

The Sponsor proposes to market the device to patients who meet the inclusion criteria as described in the first paragraph of this review. In addition to the inclusion/exclusion criteria in the Feasibility Study, the sponsor proposes the following types of patients who have contraindications to LVAD placement and who are not necessarily in biventricular failure would be included in the indications for the device:

- refractory arrhythmias: These patients "...would require biventricular support since the occurrence of arrhythmia would significantly reduce right side flow..."
- aortic regurgitation
- prosthetic aortic valve
- "Massive MI": patients who are "...at risk of inlet cannula dislodgement due to fragility of the infarcted ventricular tissue."
- Mural thrombus in the ventricles
- Ventricular septal rupture
- Transplant rejection

It should be noted that none of the 14 patients in the Feasibility Study had any of the above conditions.

The Sponsor proposes to collect the following data:

Safety: frequencies of neurologic events, infection, bleeding, renal dysfunction, liver dysfunction, and respiratory events

Efficacy: duration of support, the number of patients discharged from the hospital, frequency of excursions while in the hospital, and normal life activities for discharged patients, hemodynamic benefit, relative length of ICU stay, hospital stay, and the number of re-admissions in relationship to the length of discharged support

The Agency proposes that efficacy be tracked by assessing survival days with acceptable neurological status (modified Rankin scale or a disability scale), the ratio of in-hospital to out-of-hospital days, validated QOL instruments (such as the Kansas City Cardiomyopathy Questionnaire), and a functional capacity assessment such as 6 min walk or MVO₂. Serious adverse events should be reported. The Agency currently recommends that patients have a standardized assessment of neurological status, including cognitive function for assessment of long-term circulatory assist devices.

The Sponsor proposes to evaluate 20 consecutive patients followed while on the device.