November 19, 2010
Office of Medical Device Evaluation
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

[Classification]	Instrument & Apparatus 7 Organ function replacement device
[Generic name]	Implantable ventricular assist device
[Brand name]	DuraHeart Left Ventricular Assist System
[Applicant]	Terumo Corporation
[Date of application]	September 17, 2009 (Application for marketing approval)

[Results of deliberation]
The results of deliberation of the Committee on Medical Devices and *In-vitro* Diagnostics of the Pharmaceutical Affairs and Food Sanitation Council on November 19, 2010 are as described below.
It was concluded that the results should be reported to the Pharmaceutical Affairs Department.

It is appropriate to approve the product with a re-examination period of 7 years under the following conditions for approval. The product is classified as a biological product, but is not classified as a specified biological product.

[Conditions for approval]
The applicant is required to:

1. Perform a use-results survey in all patients including those who completed the extended clinical study in cooperation with related academic societies during the re-examination period. At the same time, observe the long-term prognosis of patients implanted with the assist device and report its analytical results.

2. Establish appropriate qualification criteria for medical institutions and physicians in cooperation with related academic societies, and take appropriate measures to limit the use of this product to physicians and medical institutions who/which understand its efficacy and safety and have sufficient knowledge and experience in surgical techniques, etc.

3. Provide sufficient training for healthcare professionals, patients, and caregivers to ensure the safe and smooth transition to home therapy. The safety of the product should be ensured by establishing a sufficient support system.

Review Report

October 29, 2010

Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following medical device submitted for registration are as follows.

[Classification]	Instrument & Apparatus 7 Organ function replacement device
[Generic name]	Implantable ventricular assist device
[Brand name]	DuraHeart Left Ventricular Assist System
[Applicant]	Terumo Corporation
[Date of application]	September 17, 2009
[Reviewing office]	Office of Medical Devices I

Review Results

October 29, 2010

[Classification]	Instrument & Apparatus 7 Organ function replacement device
[Generic name]	Implantable ventricular assist device
[Brand name]	DuraHeart Left Ventricular Assist System
[Applicant]	Terumo Corporation
[Date of application]	September 17, 2009

[Results of review]
DuraHeart Left Ventricular Assist System is an implantable left ventricular assist device intended for use to improve the blood circulation in patients with end-stage severe heart failure who require cardiac transplantation.

The data on stability and durability, and data on performance including electrical safety, biological safety, and mechanical safety were submitted as the evaluation data from the non-clinical studies. Although temporary stoppage of the pump occurred in the European clinical study, there is an attempt to improve DuraHeart by modifying the product to prevent [redacted], which was the probable cause of the malfunction.

The data from the European and Japanese clinical studies were submitted as the evaluation data from clinical studies. In the European clinical study (with 33 subjects), the survival rate at 13 weeks after implantation, which is the primary endpoint, was 81.5% (95% confidence interval [CI], 63.2%-91.2%; Kaplan-Meier test). This result met the success criterion based on the objective performance criteria (OPC) defined from the published data on the survival rate of other implantable ventricular assist devices. The survival rate at 6 months after implantation was 76.0% (95% CI, 55.1%-88.2%; Kaplan-Meier test). For safety, although serious neurological disorders related to anticoagulation and antiplatelet therapy occurred, the clinical data of the product did not demonstrate its inferiority when compared with the clinical data of similar devices. In the Japanese clinical study (with 6 subjects), the product was successfully implanted in all the subjects. No deaths were reported during the evaluation period after operation. Five of the 6 subjects were discharged from the hospital to receive home therapy. Their cardiac function and quality of life (QOL) were improved. The pump functioned normally. The number of days of circulation assist was 181 ± 8 (mean ± standard deviation) at 26 weeks after operation at which the final evaluation was made. In the European clinical study, the assist period before cardiac transplantation was 197 ± 172 days (mean ± standard deviation), with the maximum period being 711 days. The data from the European post-marketing surveillance included in the reference data revealed that some patients were assisted for more than 1600 days. The controller of this product is to be connected to 2 power supply systems, but the 2 systems were disconnected at the same time in 23 and 3 subjects in the European and Japanese clinical studies, respectively. Taking into account that no trial-related serious injury did not occur in the study subjects, the risk of the event is not unacceptable compared to the product's benefit, but this product clearly has a potential risk of the disruption of the power supply to the pump. Therefore, it was concluded to instruct the applicant to continuously seek measures to reduce

the risk and consider revising the specifications.

Based on its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the following intended use with the following conditions, taking into account that no implantable ventricular assist device is clinically available in Japan, and that the clinical efficacy and safety of this product was supported by the submitted data, and that this result should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

[Intended use]
DuraHeart Left Ventricular Assist System is used to improve the blood circulation until cardiac transplantation is performed in patients who have severe heart failure for which cardiac transplantation is indicated, and show continuous decompensation in spite of drug therapy or circulation assist techniques, such as the use of an external ventricular assist device, and whose lives cannot be saved without cardiac transplantation.

[Conditions for approval]
The applicant is required to:

1. Perform a use-results survey in all patients including those who completed the extended clinical study in cooperation with related academic societies during the re-examination period. At the same time, observe the long-term prognosis of patients implanted with the assist device and report its analytical results.

2. Establish appropriate qualification criteria for medical institutions and physicians in cooperation with related academic societies, and take appropriate measures to limit the use of this product to physicians and medical institutions who/which understand its efficacy and safety and have sufficient knowledge and experience in surgical techniques, etc.

3. Provide sufficient training for healthcare professionals, patients, and caregivers to ensure the safe and smooth transition to home therapy. The safety of the product should be ensured by establishing a sufficient support system.

Review Report

October 29, 2010

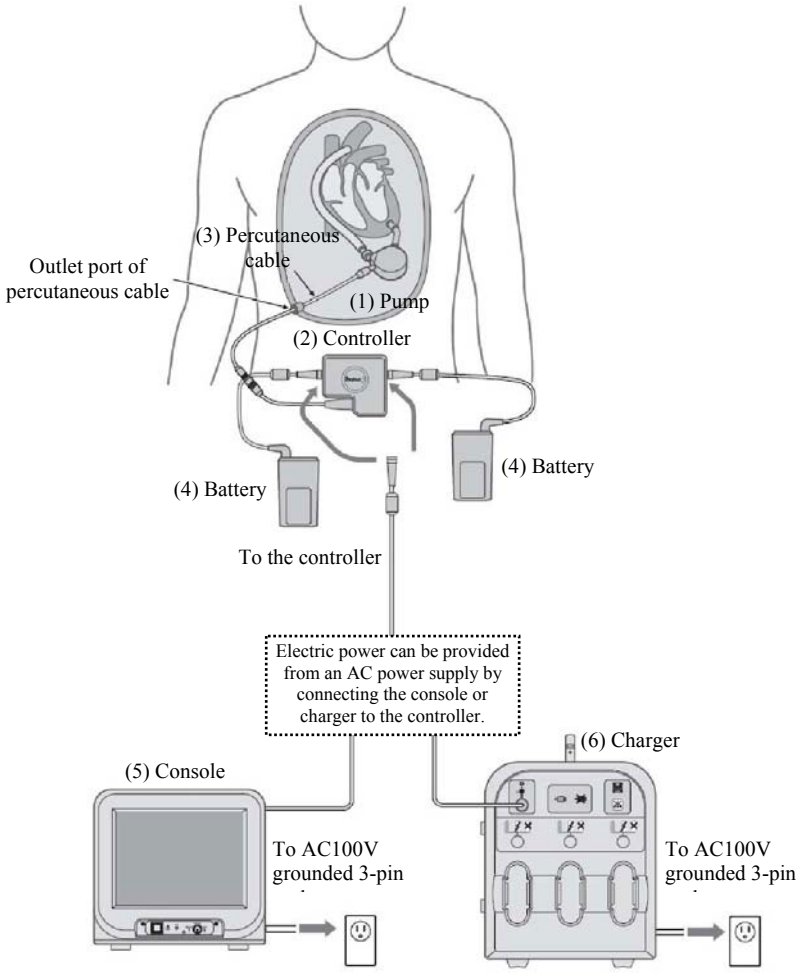
I. Product for Review

[Classification]	Instrument & Apparatus 7 Organ function replacement device
[Generic name]	Implantable ventricular assist device
[Brand name]	DuraHeart Left Ventricular Assist System
[Applicant]	Terumo Corporation
[Date of application]	September 17, 2009
[Proposed intended use]	This product is an implantable left ventricular assist device intended for use to improve the blood circulation in patients with end-stage heart failure who require cardiac transplantation.

II. Product Overview

DuraHeart is an implantable left ventricular assist device intended for use to improve the blood circulation in patients with end-stage severe heart failure who require cardiac transplantation. It consists of an implantable pump, a percutaneous cable connecting the pump and controller, an extracorporeal controller, batteries, a console, and a charger. The pump is a centrifugal pump with an impeller controlled by a magnetic levitation system. In a case where failure in the magnetic levitation mechanism occurs and it cannot automatically return to normal operation, the pump can continuously operate by the hydrodynamic levitation resulting from dynamic pressure grooves in the pump chamber and impeller rotation. Blood flowing from the left ventricular apex through the inflow conduit to the pump is delivered to the ascending aorta via the outflow conduit by the motorized rotating impeller. The percutaneous cable connects the pump and controller through the patient's skin to supply electric power and transmit control signals to the pump. The controller placed outside the body is responsible for controlling pump motor rotation and impeller magnetic levitation, monitoring the pump operation and controlling power supply to the pump, and provides a user interface. The controller has other functions including storing parameters for individual patients, such as the target rotational speed, and recording pump operation status and malfunction history. The pump can receive electric power from the batteries, console, or charger. It is always connected to 2 systems of power supply. Only one of the power supply systems is used, and switches automatically to the other system if any malfunction is detected on the one currently used. Each battery is a portable, rechargeable unit based on lithium ion secondary batteries. It has various functions including not only power supply, but also the battery remainder indication, charging and discharging frequency counting, data communication, [redacted], and an alarm. It also has safety functions including overcurrent protection at discharge, over-discharging protection, output short-circuiting protection, and overcharging protection. The console is used in the hospital to set up, adjust, monitor, and trouble-shoot the device. It also supplies the device with electric power. The charger is connected to an AC commercial power source to recharge up to 3 batteries at a time. In addition to the charge function, it supplies electric power to the pump via the controller. Electric power is supplied from the batteries or charger when the patient is at home.

Figure 1. System Structure and Appearance



III. Summary of the Submitted Data and the Outline of Review by the Pharmaceuticals and Medical Devices Agency

The data submitted by the applicant in the application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

The expert advisors for the Expert Discussion on this product declared that it does not fall under the Item 5 of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/20 dated December 25, 2008) .

1. Origin or history of discovery and usage conditions in foreign countries etc.

[Origin or history of discovery]

Approximately 15 million people suffer from heart failure in the world, 5% of whom have end-stage heart failure[1,2]. More than 5 million people suffer from heart failure in the US, and half of the patients diagnosed with end-stage heart failure die within 5 years[1,2]. Only limited therapeutic options are available for patients with end-stage heart failure. Cardiac transplantation is now the gold standard or a preferred option. The Organ Procurement and Transplantation Network (OPTN) reported that about 3500 patients were newly registered to the waiting list of cardiac transplantation in 2009, while the 2009 database of the International Society for Heart & Lung Transplantation (ISHLT) showed that there were less than 2100 heart donors in the US. Similarly, only a small number of donor hearts have been supplied in Japan; only 64 patients have received cardiac transplantation as of October 2009 since the enforcement of the Act on Organ Transplantation[3] in October 1997. Although it is estimated that there are 228 to 670 patients with an indication for cardiac transplantation per year, only 5 to 11 patients per year received cardiac transplantation in the last five years in Japan[3]. It was reported that the mean waiting period for patients who received cardiac transplantation was 883 days (29-2747 days), the mean waiting period for patients in urgent status (Status 1) was 791 days (29-1390 days), and the mean period on a heart assist device was 807 days (20-1446 days) in Japan. These periods are longer than the waiting period for patients in Status 1 (56 days) and the waiting period on a mechanical assist device (50 days) in the US[3].

Novacor Left Ventricular Assist System (approval number, 21300BZY00468000, Edwards Lifesciences; hereinafter called Novacor) and implantable ventricular assist system HeartMate XVE LVAS (approval number, 22100BZY00011000, Nipro Corporation; hereinafter called HeartMate XVE) were approved in 2001 and 2009, respectively. However, both of them are indicated in only a limited number of patients due to the large pump size. Since Novacor is no longer commercially available and HeartMate XVE has not been released, no implantable ventricular assist device is currently available in Japan. Therefore, there is a strong need for circulation assist therapy using an implantable ventricular assist device that can improve and maintain blood circulation in patients with end-stage severe heart failure. Especially in Japan, high-performance implantable ventricular assist devices are required that (a) can be used for a long waiting period for transplantation, (b) cause less complications, allow patients to be treated at home, and can maintain high QOL and (c) are small in size and suitable for the Japanese physical constitution. Under such circumstances, the applicant decided to apply their centrifugal pump technology for extracorporeal circulation to develop an implantable ventricular assist device. Rotational power transmission in the centrifugal pump is achieved by a magnet coupling between the magnets embedded in the impeller and directly attached to the motor. At the beginning of development, the shaft and bearing ensured the stable rotation of the rotating part,

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[1] Deng MC, et al. Mechanical Circulatory Support Device Database of the International Society for Heart and Lung Transplantation: Third Annual Report-2005. *J Heart Lung Transplant*. 2005; 24(9):1182-1187.

[2] Taylor DO, et al. Registry of the International Society for Heart and Lung Transplantation: Twenty-second Official Adult Heart Transplant Report-2005. *J Heart Lung Transplant.* 2005;24(8):945-955.

[3] Committee on Public Information, Japan Society for Transplantation: *Organ Transplantation Fact Book 2009*

and the seal material separated the magnets from blood. However, there were cases where malfunction occurred due to material deterioration etc, caused by rotational friction between the shaft and the seal material when the mechanical assist was prolonged. The applicant therefore modified the structure and functions of the centrifugal pump to prevent such failures and finally developed DuraHeart as a small and lightweight ventricular assist device that can be used for a long time without rotational friction, blood damage, thrombus formation, or cavitation.

[Usage conditions in foreign countries and Japan]
DuraHeart received CE Marking in Europe on February 26, 2007 and the cumulative sales quantity as of August 31, 2010 is [redacted]. At that time point, the malfunctions reported to the European regulatory authorities from patients including those who completed the observation period of the European clinical study included (a) 1 event of a charger power supply failure (1 of 94 patients), (b) 1 event of a delay in the response to, and replacement of, the controller that generated an alarm (1 of 94 patients), and (c) 5 events of 3 types of pump impeller failures (5 of 94 patients).

(a) The charger electric supply failure resulted from the short circuit associated with the fracture of [redacted] at the power supply unit. Investigations showed that there was no problem in the manufacturing records of the product that had the failure. There was no adverse effect from the physical stress during the assembly process either. Although the cause of the fracture of [redacted] remains unknown, the manufacturer, Terumo Heart Inc., considered that the failure had no deleterious impact on the other lots since no similar events have occurred so far and the incidence of malfunctions at the supplier of the power supply unit was 0.013% (2 events of 150,000 units) during the last 7 years. The present malfunctions did not cause any trial-related injury to the patient.

(b) The healthcare professional failed to immediately replace the controller that generated an alarm (for the power shutdown by the protective circuit). This event did not cause any trial-related injury to the patient. The medical institution and patient had been trained on measures to be taken against the alarm. The measures were specified in the operating instructions as well. After this event, the manufacturer, Terumo Heart Inc., re-trained the medical institution on how to respond to the alarm, and added precaution statements to the operating instructions as the safety information for medical institutions and patients. Since then, no similar malfunctions have been reported.

(c) For the 5 events of 3 types of pump impeller failures, a magnetic levitation error occurred inferred to be due to the poor connection of the part related to the magnetic levitation sensor. The pump was eventually removed and another new pump was implanted in the affected patients. The first type (2 events) of the three was estimated to be a result of the poor contact between [redacted] and [redacted] of [redacted] of the controller and pump. Therefore, the inspection of [redacted] of [redacted] and [redacted] was added to the manufacturing process and was included in the specifications. Further, a jig was added to ensure electric connection. No similar events have been reported since the improvement. The second type (2 events) occurred from a breakage of the magnetic levitation sensor line. Since the breakage was confirmed to result from fatigue fracture, a verification test to simulate the unexpected stress on the pump cable was performed. The third type (1 event) occurred when the [redacted] in the pump cable partially broke, resulting in the contact with the circuit lead in the cable. It was confirmed that the failure resulted from fatigue fracture. Since the third type of failure seemed to occur by the same mechanism as the second type of failure, it was verified by performing a similar test.

In addition, a breakage of the magnetic levitation sensor line occurred in a foreign country on September 2, 2010. The mechanism of the breakage is being investigated, and the applicant now

considers that it is the same phenomenon as the second type of failure in the above (c).

PMDA asked the applicant to explain the verification test results and measures taken for the breakage of the magnetic levitation sensor line.

The applicant responded as follows:
The verification test results showed that the event resulted from excessive bending of or strong stress on the pump cable. Therefore, the instructions for use will be added with the following preventive measures: not to handle the pump only with the percutaneous cable and not to bend the percutaneous cable before or during the implantation of the pump. The same cautions were also given during training.

PMDA accepted the explanation of the applicant since it was considered possible to prevent the breakage of the pump cable from excessive bending or strong stress by giving cautions in the instructions for use and during training. For the breakage of the magnetic levitation sensor line that occurred on September 2, 2010, there is no sufficient information on the event at present. PMDA instructed the applicant to continue to collect the information and analyze the cause of the event and to take measures, as required. The details and results of clinical studies are described below in "Clinical Data."

2. Setting of specifications

Specifications of characteristics/performance or functions are set for the pump, controller, battery, charger, console, emergency battery, and shower bag separately. Those of the pump include method, discharge rate range, use environment, and pump characteristics. Those of the controller include the target rotational speed setting range, rotation control accuracy, magnetic levitation control function, flow rate calculation function, pump correction function, display items, multilingual environment, power supply change-over function, operation history record function, self-diagnosis function, notification sound function, alarm function, safety device, alarm muting function, alarm clearing function, use conditions (ambient temperature, relative humidity, atmospheric pressure), and storage conditions (ambient temperature, relative humidity). Those of the battery include the power supply function, battery remainder indication function, charging and discharging frequency counting function, data communication function, [redacted], alarm function, safety device, use conditions (ambient temperature, relative humidity, atmospheric pressure), and storage conditions (ambient temperature, relative humidity). Those of the charger include the charging function, power supply function, alarm function, safety device, alarm muting function, use conditions (ambient temperature, relative humidity, atmospheric pressure), and storage conditions (ambient temperature, relative humidity). Those of the console include the pump parameter setting function, rotational speed setting range restricting function, controller alarm clearing function, controller setting function, pump activation/termination function, display items, user restricting function, console adjusting function, date and time synchronization function, multilingual environment, data storage function, [redacted], update function, self-diagnosis function, power supply function, alarm function, safety device, alarm muting function, alarm clearing function, battery pack standby mode, use conditions (ambient temperature, relative humidity, atmospheric pressure), and storage conditions (ambient temperature, relative humidity). Those of the emergency battery include the power supply function, use conditions (ambient temperature, relative humidity, atmospheric pressure), and storage conditions (ambient temperature, relative humidity). Those of the shower bag include the liquid protection function.

Quality specifications of characteristics/performance, functions, and safety are set for the pump, inflow conduit, apical cuff, outflow conduit, controller, battery, charger, and console, separately. Those of the pump include pump surface temperature increase test, ultrasonic energy exposure test, pump durability test, percutaneous cable (pump/controller side) durability test, pump fluid

characteristics test, [redacted], [redacted], *in vitro* pump hemolysis test, pump mechanical disturbance test, [redacted], and heparin activity. Those of the inflow conduit include heparin activity. Those of the apical cuff include apical-cuff suture retention test, apical-cuff quality test – appearance, apical-cuff quality test – relaxed internal diameter, apical-cuff quality test – usable length, apical-cuff quality test – burst strength test, apical-cuff quality test – water permeability test, and apical-cuff quality test – whole graft porosity test. Those of the outflow conduit include outflow conduit tensile test, outflow conduit anti-kink protective cover radial force test, quality test of the outflow conduit – appearance, quality test of the outflow conduit – relaxed internal diameter, quality test of the outflow conduit – usable length, quality test of the outflow conduit – burst strength test, quality test of the outflow conduit – water permeability test, quality test of the outflow conduit – whole graft porosity test, and heparin activity. Those of the controller include [redacted] test, [redacted] test, [redacted] test, [redacted] test, [redacted] test, test for acoustic noise during operation, and operational random vibration test. Those of the battery include [redacted] test, operational random vibration test, and [redacted] test. Those of the charger include [redacted] test and noise limit regression test. Those of the console include [redacted] test, [redacted] test, [redacted] test, and noise limit regression test. In addition, the following specifications were established and the data to validate them were submitted: electrical safety (IEC60601-1 1988, Amendments 1, 2) and electromagnetic compatibility (IEC60601-1-2: 2007), extractable particle test, bacterial endotoxin test, sterility assurance level (SAL) and validation method (ISO11135), residual ethylene oxide and ethylene chlorohydrin (ISO10993-7), biological safety (ISO10993).

PMDA accepted the established specifications and specification limits as appropriate on the condition that appropriate product specifications were added, based on the discussion in the "Performance" section below.

3. Stability and durability

Stability data related to DuraHeart were submitted including activity of heparin used for heparin coating, shelf life test results of the battery, and shelf life test results of the console battery. Basically, all the raw materials used for the product parts that come in contact with blood or body fluid are assured of being stable since they are used in approved medical devices to be implanted in the body or [redacted] for which [redacted] specifications are established. A heparin coating long-term stability test was performed using heparin activity as an index since maintaining [redacted] was considered important for the efficacy and safety of the product. The test results confirmed stability for at least 2 years. The above battery shelf life tests were performed to confirm that the battery would not deteriorate. The test results showed no particular problems.

Durability data including pump and percutaneous cable (pump/controller sides) durability test results, battery capacity test results, outflow conduit durability test results for bending resistance, and transportation test results were submitted. The pump durability test showed a reliability of 84.8%, which is above the target value of the reliability test specified by the American Society for Artificial Internal Organs and American Association for Thoracic Surgery, which is a reliability of at least 80% at a confidence level of 80% after a 1-year operation.

PMDA asked the applicant to explain the following 2 points:

(1) Evaluation of reliability after at least a 2-year operation based on the results of the pump durability test which was ongoing at the time of new medical device application since the waiting time for cardiac transplantation may exceed 2 years in Japan.
(2) Appropriateness of performing the durability tests using a steady flow test system against the supposition that patients implanted with the product will receive blood in a pulsatile

flow.

The applicant responded as follows:

(1) As a result of pump durability test after a 2-year operation, the tested pumps had no failure at all during the test period and showed a reliability of 84.7%, which was above the target value specified by the associations, i.e., reliability of at least 80% at a confidence level of 80% after a 2-year operation.

(2) The durability tests were performed using a steady flow test system since more devices are required to maintain the test system under the pulsatile flow than steady flow condition, which might increase unstable factors, such as failure of the testing device. DuraHeart is a system that performs [redacted] of [redacted] at far shorter intervals ([redacted] times/second) than [redacted]. The results of pump mechanical disturbance test, which were submitted as the "Performance" data mentioned below, showed that the product operated normally even when a mechanical disturbance at a far higher acceleration than the change in blood flow was given. These results assure the durability of the product against mechanical disturbance. It is therefore considered acceptable to use the product under a pulsatile flow condition.

PMDA concluded that there were no major problems about pump durability, considering that it is difficult to perform a long-term pulsatile flow test, that no problem occurred in the mechanical disturbance test under long-term pump operation, and that no particular problems were observed from the clinical study results of the product or use results in foreign countries, although it should be noted that the submitted pump durability test results did not directly indicate the long-term use results of the product in a pulsatile flow.

4. Conformity to the requirements specified in Paragraph 3 of Article 41 of the Pharmaceutical Affairs Act

A declaration of conformity declaring that the product meets the standards for medical devices as stipulated by the Minister of Health, Labour, and Welfare in accordance with Paragraph 3 of Article 41 of the Pharmaceutical Affairs Act (hereinafter referred to as “the Essential Principles”) (MHLW Ministerial Announcement No. 122, 2005) and the Ministerial Ordinance on Quality Management System for Medical Devices and *In Vitro* Diagnostics (MHLW Ministerial Ordinance No. 169, 2004) was submitted.

PMDA reviewed the conformity to the standards specified in Paragraph 3 of Article 41 of the Pharmaceutical Affairs Act and accepted the declaration.

5. Performance

[Physicochemical properties]

As the data on physicochemical properties, the results of tests included in the quality specifications were submitted. PMDA confirmed that all the test results met the specifications and therefore accepted the test results.

[Electrical safety and electromagnetic compatibility]

As the data on electrical safety, the results of tests included in the quality specifications were submitted. It was shown that all the items met the specifications.

As the data on electromagnetic compatibility, in addition to the results of tests included in the quality specifications, the Field EMC test results using devices that the product might encounter in daily life situations were submitted. It was shown that the test results met the quality specifications. On the other hand, in the Field EMC test on compatibility with an IH rice steamer, a levitation error alarm indicating impeller levitation position abnormality was issued when the pump [redacted] faced towards the steamer and was brought closer to the steamer to a

distance of about [redacted] cm. The pump then transferred to performance under hydrodynamic levitation condition and maintained circulation. No effect of the IH rice steamer was observed after the pump transferred to the performance under hydrodynamic levitation condition. In the compatibility test with an electromagnetic cooker, a levitation error alarm indicating impeller levitation position abnormality was issued when the pump [redacted] was brought closer to the center of the cooker to a distance of [redacted] cm. The pump then transferred to performance under hydrodynamic levitation condition and maintained circulation. When the pump [redacted] was brought closer in the same manner, a levitation error alarm indicating impeller levitation position abnormality was issued at a distance of [redacted] cm. The pump transferred to performance under hydrodynamic levitation condition and maintained circulation. In either case, the pump was not affected by the electromagnetic cooker after it transferred to the pump performance under hydrodynamic levitation condition. Although the precautions on various electromagnetic sources are already described in the instructions for use, it was decided from the above test results that the Warnings section of the instructions for use would be revised to include the cautions that IH rice steamers and electromagnetic cookers should be used out of the reach of the patient, or should not be used.

PMDA asked the applicant to explain how patient safety would be secured when the product operated improperly since improper operation, if any, might directly affect a patient's life.

The applicant responded as follows:
It was verified that the product would operate normally with electromagnetic devices it might encounter during daily life. However, [redacted] central processing units (CPUs) were equipped in the control unit of the controller to increase the resistance to failures in preparation for unexpected problems. When the device operates improperly due to external effects, the controller detects abnormal signs and issues an alarm to warn the patient. When the controller detects an abnormal state from the abnormal sign, the safety devices are automatically activated to maintain the assisted circulation. When abnormality is detected in one of the 2 systems of electric power supply connected to the controller, the controller switches power supply to the other system to maintain the assisted circulation, and issues an alarm to make the patient take actions. Since a series of these operations have been verified and confirmed to have no problem, patient safety is assured even when the product operates improperly by external effects.

PMDA accepted the response taking into account that the product was designed in consideration of the reduction and management of improper operations and a series of the operations were verified and confirmed to have no problem as well, although the possibility that the improper operations of the product by external effects could not be denied.

[Biological safety]
Biological safety tests were performed to confirm that the parts of the product components that come in contact with circulating blood comply with the latest biological safety guidelines. Raw material sections prepared according to the proportion of the surface area of the product that comes in contact with blood or tissue were used as test samples. Raw materials for which biological safety were assured from previously approved products were included. The following biological safety tests were performed according to ISO 10993-1: cytotoxicity test, skin sensitization test, intracutaneous reactivity test, acute systemic toxicity test, pyrogenicity test, hemocompatibility test (hemolysis), hemocompatibility test (coagulation/platelet), hemocompatibility test (complement), genotoxicity tests (reverse mutation), genotoxicity test (micronucleus), genotoxicity test (mouse lymphoma), subacute systemic toxicity test, and chronic toxicity test. All the test results except for implant test results showed no particular problems and these test results were submitted.

The applicant explained the implant test results as follows:

Mild positive reactions were observed with a sample of the raw material used for the artificial graft (woven) part of the outflow conduit and samples of the raw material used for the fabric cable cover and apical cuff of the pump, but these samples were not as smooth as the high-density polyethylene sheet used as the negative control. They had fine cavities resulting from the woven structure. It is generally known that the implantation of materials with a woven structure causes tissue reactions including the appearance of macrophages and foreign-body giant cells associated with granulation and organogenesis, which is consistent with the findings from the implant test. The applicant therefore considered that the observed positive reactions are not biologically significant.

PMDA reviewed the biological safety data and accepted the applicant's view that the biological safety of the product was assured.

[Mechanical safety]
As the data on mechanical safety, the results of tests included in the quality specifications were submitted. These results showed no particular problems and PMDA accepted them.

[Other performance evaluation]
In addition to the above mentioned performance characteristics, the following tests and analyses included in the quality specifications were performed and their results were submitted as the data for evaluating other performance: random vibration test, [redacted] test, and flow estimation test for the product; *in vitro* pump hemolysis test, pump fluid characteristics test, and mechanical disturbance test for the pump; test for acoustic noise during operation for the controller; [redacted] function test, internal battery-maintains-charge test (on connecting AC line), [redacted] function test, and noise limit regression test for the console; protection against battery short circuit test, charge characteristics test, and noise limit regression test for the charger; battery running time test, battery indicator display test, external battery communication functions test, [redacted] test, and short circuit test for the battery; discharge capacity test for the emergency backup battery; outflow conduit tensile test, outflow conduit anti-kink protective cover radial force test, and apical-cuff suture retention test for the inflow conduit, apical cuff, and outflow conduit; and [redacted] test for the shower bag. Further, an *in vivo* chronic performance test in animals and pump fluid analysis, which are not included in the specifications, were also performed and the results were submitted.

The *in vivo* chronic performance test in calves was an *in vivo* study conducted according to GLP regulations to demonstrate the compatibility of the product for human use by implanting the product in 12 calves and operating the product for 60 days (recommended period in ISO/TC150/SC6/WG6 Electromechanical Cardiac Circulatory Systems). Five of the 12 animals experienced postoperative complications. Four of the 5 animals developed myocardial thrombus formation or ventricular septum wall laceration since it was anatomically difficult to position the inflow conduit. The complications were therefore considered not relevant for human use. The remaining 1 animal had a complication found to result from a manufacturing failure of the motor [redacted] and was therefore excluded. Blood flow was maintained and no failure developed during the study period for the 7 surviving animals.

PMDA examined whether the performance of the product could be fully evaluated with the above test results or not and asked the applicant to additionally evaluate the following issues: (1) no occurrence of vibration-induced loose connection between the inflow or outflow conduit and pump, (2) no leakage from the connection, (3) appropriate strength of the inflow conduit, (4) appropriate strength of the battery connection and maintenance of electric connection, and (5) [redacted] test results for [redacted] and [redacted] added to the manufacturing process to prevent the magnetic levitation errors estimated to result from poor electric connection of the magnetic

levitation sensor, as explained in the "Origin or history of discovery and usage conditions in foreign countries etc." section.

The applicant demonstrated the (1) no occurrence of the loose connection between the inflow or outflow conduit and pump by submitting the random vibration test results obtained by the method in accordance with ISO14708-1; (2) no leakage from the connection by submitting the positive pressure test results as obtained by applying a pressure of [redacted] mmHg to the test solution storage tank; (3) appropriate strength of the inflow conduit by submitting the tensile, torsion, and flexion test results of the inflow conduit; (4) appropriate strength of the battery connection and maintenance of electric connection by providing the strength test results as obtained by applying a load of [redacted] kg; and (5) validity of the [redacted] test for [redacted] and [redacted] by submitting the [redacted] test results of the electric connection [redacted] in the pump.

PMDA reviewed and accepted the data on performance and concluded that the additional data can be used to evaluate the issues on performance that could not be fully evaluated with the data submitted at the time of regulatory submission.

6. Risk analysis

Documents summarizing the risk management system and its implementation status in reference to ISO 14971, which is a standard on the application of risk management to medical devices, were submitted.

PMDA reviewed and accepted the risk analysis data.

7. Manufacturing process

[Sterilization method and sterilization validation]

Data on sterility assurance level, sterilization parameters, residual ethylene oxide, and ethylene chlorohydrin were submitted as sterilization method information. PMDA accepted them.

[Safety of heparin]

[redacted] heparin [redacted], which is the main raw material of the coating, is manufactured by [redacted] USP heparin sodium by [redacted]. Heparin used for manufacture is derived from [redacted] of healthy [redacted] from [redacted]. Donor animals are confirmed to be healthy and compatible for [redacted] use by the examinations before and after slaughtering. To inactivate/remove pathogens in the heparin manufacturing process, [redacted] (pH [redacted], [redacted] hours), [redacted] processing ([redacted]% [redacted], pH [redacted], [redacted]ºC, [redacted] hours), and [redacted] processing ([redacted] ppm, pH [redacted], [redacted] hours, followed by neutralization with [redacted]% [redacted]% sulfite for [redacted] hours) are performed. Among the above processes, the [redacted] and [redacted] processing were subjected to virus validation testing. Related viruses of [redacted], [redacted], and [redacted] were selected as model viruses and provided viral clearance indexes of ≥[redacted], ≥[redacted], and ≥[redacted] for [redacted] processing, ≥[redacted], ≥[redacted], and ≥[redacted] for [redacted] processing, and ≥[redacted], ≥[redacted], and ≥[redacted] for the total. These results confirmed the ability of the processes to inactivate/remove viruses. The information for assuring the quality and safety of heparin is promptly available, as required.

Based on the above facts, the applicant explained that heparin complies with the Standards for Biological Ingredients (MHLW Ministerial Announcement No. 210, 2003); Standards for Animal Derived Materials, and that the safety of heparin was therefore assured. PMDA accepted the explanation.

[Safety of gelatin]
Gelatin used for the sealing process is derived from healthy bovine bones originating from Australia. It is manufactured using bovine bones collected by taking preventive measures against the entry of raw materials derived from BSE (bovine sponge encephalopathy) infected animals or bones from sites prohibited by the Standards for Ruminant Animal Derived Materials of the Standards for Biological Ingredients (except spinal bone, trigeminal ganglions, and dorsal root ganglions) into the manufacturing process. Gelatin therefore falls into the category of highly purified products. Based on these facts, the applicant explained that gelatin complies with the Standards for Ruminant Animal Derived Materials of the Standards for Biological Ingredients, and PMDA accepted the explanation.

8. Clinical data

The data from the European and Japanese clinical studies were submitted. The results from the European post-marketing surveillance, US clinical study, and Japanese extended clinical study were submitted as reference data.

[European clinical study]
The European clinical study was performed to evaluate the safety and performance of DuraHeart in the treatment of patients with end-stage severe heart failure from January 15, 2004 to June 15, 2007 (the study was intermitted from October 18, 2004 to January 31, 2005 to analyze the cause of temporary stoppage of the pump in patients implanted with the A motor. Eventually, the study was performed in 16 patients implanted with the A motor and 17 patients implanted with the B motor). The primary endpoint of the study was the survival rate at 13 weeks after implantation (survival to cardiac transplantation if cardiac transplantation was performed before 13 weeks after implantation), which was evaluated in comparison with OPC (70%) determined based on the published survival data of other implantable ventricular assist devices. The secondary endpoints of the study, throughout the follow-up period, were (1) safety evaluation based on the analysis of adverse events, technical events, death rate, and findings after the removal of the pump, (2) functional evaluation of the pump, and (3) evaluation of the general conditions of patients. The applicant planned that the sample size of the study would be at least 20 subjects considering the feasibility, from including the fact that the sample size of European studies of other implantable ventricular assist devices was approximately 20 subjects. The equivalence to existing implantable ventricular assist devices was planned to be verified using a clinically significant difference (δ) of 27%, but in actuality, total of 33 subjects were enrolled. For the demographics of the 33 subjects, the mean age was 55.1 years (29-73 years) and body surface area (BSA) was 1.90 (1.40-2.40). The proportion of male subjects was 85%. Primary diseases included idiopathic cardiomyopathy in 42.4%, ischemic heart disease in 42.4%, hypertrophic cardiomyopathy in 9.1%, and others in 30.3%.

Twenty seven of the 33 subjects (82%) achieved the primary endpoint. Six subjects died before achieving the endpoint. The estimated survival rate at 13 weeks as determined by the Kaplan-Meier test was 81.5% (95% CI, 63.2%-91.2%) and the lower limit of the confidence interval exceeded 43% (OPC-δ). It was therefore confirmed the success criterion based on the comparison with the predefined OPC was met. The estimated survival rate in the A motor group (16 subjects) was 62%, while that in the B motor group (17 subjects) was 100% (P = 0.006; log-rank test).

For the safety evaluation in the secondary endpoints, all the adverse events observed during the follow-up period are presented in Table 1. Those evaluated as related to the product are presented in Table 2. The time-series distribution of adverse events is shown in Figure 2. Technical events are presented in Table 3. The relationship between the product and cause of

death as judged by the Clinical Event Committee (CEC) is shown in Table 4, where the cause of death is defined as an "event most closely related to death." Ten subjects died during the study period including the follow-up period and a causal relationship to the product could not be denied in 6 subjects (60%) and, deaths in 4 subjects (40%) were judged unrelated to the product. There were no deaths that were judged related to the product. Cerebrovascular accident (CVA) was determined to be the cause of death in 4 subjects, although the 4 subjects had not only neurological dysfunction, but also other complications and serious infections. Sepsis caused death in 3 subjects. The remaining 3 subjects died of other causes. The review of available autopsy reports showed no specific tendency in the cause of death. The cause of death were not related to the [redacted] motor type (A or B motor).

Table 1. Adverse events (European clinical study)

Adverse event	**Number of subjects (N [rate])**	(serious)	**Number of events**	(serious)
All adverse events	31 (94%)	(28 [85%])	135	(96)
Infections	21 (64%)	(19 [58%])	35	(25)
Arrhythmia	14 (42%)	(11 [33%])	17	(11)
Neurological dysfunction	10 (30%)	(9 [27%])	11	(10)
Right heart failure	9 (27%)	(9 [27%])	10	(10)
Haemorrhage	8 (24%)	(8 [24%])	8	(8)
Renal failure acute	6 (18%)	(4 [12%])	6	(4)
Respiratory failure	5 (15%)	(4 [12%])	5	(4)
Device failure: Temporary stoppage of the pump	2 (6%)	(2 [6%])	3	(3)
Hepatic insufficiency	2 (6%)	(2 [6%])	2	(2)
Others (pleural effusion, reoperation, and drug-induced thrombocytopenia, etc.)	21 (64%)	(14 [42%])	38	(19)

Adverse events that developed up to 30 days after cardiac transplantation included primary transplant heart failure, sepsis, cardiogenic shock, infections, and reoperation.

Table 2. Summary of adverse events assessed as related to DuraHeart (European clinical study)

Adverse event	**Number of subjects** (N [rate])	**Number of events**
Infections	10 (30%)	12
Serious infections	7 (21%)	8
Haemorrhage	4 (12%)	4
Device failure: Temporary stoppage of the pump	2 (6%)	3
Right heart failure	1 (3%)	1
Others : syncope and poor inflow conduit positioning	2 (6%)	2

Figure 2. Incidence of adverse events for a specific period of time after implantation (European clinical study)

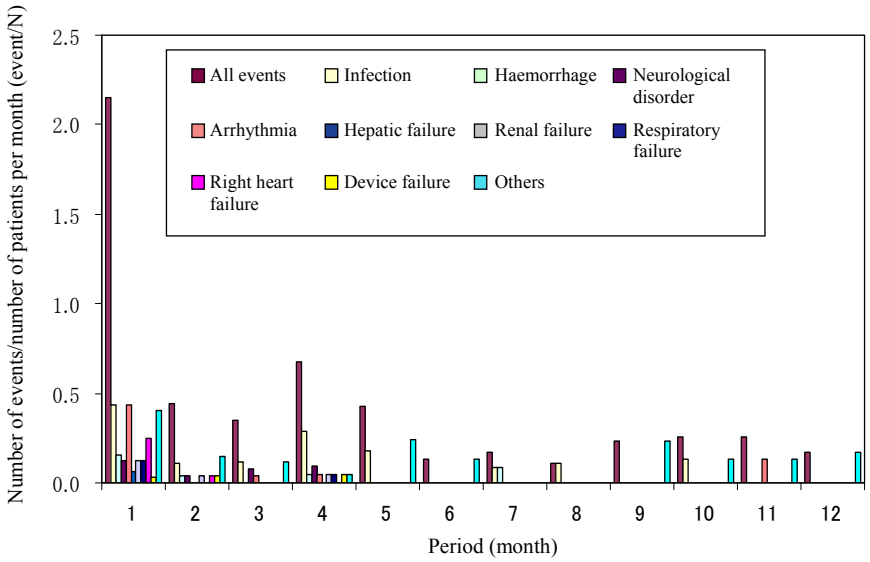

Table 3. Summary of technical events (European clinical study)

Event	Number of subjects	Number of events	Expected/ unexpected event	Serious event (event)	Comment
Disconnection of both power supplies	23	70	Expected event	0	All poor cable connections leading to “automatic restart” immediately after the temporary stoppage of the pump
Cable disconnection	10	11	Expected event	0	All poor cable connections leading to “automatic restart” immediately after the temporary stoppage of the pump
Software update	6	6	Expected event	1	Normal pump operation was maintained in all the controllers. No urgent disorder occurred.
Controller replacement	14	17	Expected event	0	Normal pump operation was maintained in all the controllers. No urgent disorder occurred.
Pump replacement	2	2	Expected event	2	After the pump temporarily stopped, each subject restarted pump operation. Subsequently, pump replacement was decided.

Table 4. Summary of deaths (European clinical study)

Age at death **Motor**	**Number of days with ventricular assist**	**Cause**	**Adverse event in ventricular assist period**	**Causal relationship to device judged by CEC** (Applicant's view)
Six subjects who died before the endpoint				
67 A	28	Neurological dysfunction (CVA)	Renal failure acute, heparin-induced thrombocytopenia, local (urinary tract) infection, ventricular arrhythmia	Not excluded
60 A	29	Neurological dysfunction (CVA)	Ventricular arrhythmia, hepatic insufficiency, local (lung) infection, pleural effusion, right heart failure, ileus	Not excluded
63 A	21	Subdural haematoma	Haemorrhage (perioperative), right heart failure, respiratory failure, local (lung) infection, renal failure acute	Unrelated (the event might result from anticoagulant therapy)
72 A	17	Cardiovascular insufficiency, subarachnoid haemorrhage		Not excluded
66 A	86	Neurological dysfunction (CVA)	Infection (sepsis), pneumothorax	Not excluded
56 A	37	Neurological dysfunction (CVA)	Infection (sepsis), effusion	Not excluded
One subject who died after 13 weeks after implantation				
61 *	178*	Infection (sepsis)	Ventricular arrhythmia, local (lung) infection, respiratory failure, device failure, pleural effusion, renal failure acute, local (large intestine) infection, anaemia, diffuse gastritis, drug-induced thrombocytopenia, depression	Unrelated (resulting from pneumonia)

Age at death Motor	Number of days with ventricular assist	Cause	Adverse event in ventricular assist period	Causal relationship to device judged by CEC (Applicant's view)
Three subjects who died after cardiac transplantation				
68 A	139	Primary transplant heart failure, sepsis	Neurological dysfunction (CVA), drug-induced leukopenia, neurological dysfunction (TIA) [POD139 transplant, POD141 death]	Unrelated (the event might be related to the drug for acute rejection)
49 A	43	Infection (sepsis)	Ventricular arrhythmia, percutaneous cable exit infection, device failure, low flow rate [POD43 transplant, POD44 death]	Unrelated (tendency of sepsis was observed even before implantation)
61 B	46	Infection (sepsis)	Ventricular arrhythmia, right heart failure, percutaneous cable exit infection, cardiogenic shock, reoperation (abdomen) [POD46 transplant, POD53 death]	Not excluded

* The pump was exchanged from the A motor (108 days) to B motor (70 days).

TIA: Transient ischaemic attack, POD: post-operative day

The stoppage of the pump occurred a total of 3 times in 2 subjects. The temporary stoppage of the pump/automatic restoration resulted in blood circulation disorder. Both of the subjects received pump replacement surgery. The temporary stoppage of the pump/automatic restoration is a controller function for recovery when impeller rotation cannot be maintained due to pump motor and magnetic levitation abnormality. In the pump motor control circuit, the rotational speed was detected by using [redacted] and the applicant considered that [redacted] and the event of the temporary stoppage of the pump/automatic restoration occurs when [redacted]. It is considered very rare for this event to occur since [redacted], it cannot be denied that some external factors possibly affected the 2 subjects observed this time. However, [redacted] after strictly controlling [redacted], in the inspection during the manufacturing process specified in the specifications, all pump motors [redacted]. No stoppage of the pump associated with [redacted] due to [redacted] has occurred since the measures.

For pump function evaluation, which is one of the secondary endpoints, the mean pump flow rate was maintained at 5.0 ± 1.0 L/min (3.3-7.4 L/min) and the mean pump index was 2.7 ± 0.5

L/min/m^2 (1.7-4.0 L/min/m^2), on Day 1 after operation. The mean pump index was above an indicator value (2.5 L/min/m^2). Although the pump index was less than 2.0 L/min/m^2 in 2 subjects, this value was derived by the general conditions of the subjects etc., and was considered acceptable since the 2 subjects had favorable outcomes. The mean pump flow rate was 5.1 ± 0.8 L/min (3.1-7.7 L/min) and pump index was 2.7 ± 0.4 L/min/m^2 (1.7-4.1 L/min/m^2) during the 12-month follow-up period. The mean pump motor rotational speed was 1652 ± 120 rpm (1319-2176 rpm) and current value was 0.58 ± 0.08 A (0.4-1.0 A).

For the general condition of patients, which is another secondary endpoint, the outcomes of subjects as of June 15, 2007 are shown in Table 5. The mean number of days of ventricular assist was 149 days (17-497 days) for the A motor and 229 days (46-711 days) for the B motor. The cumulative number of days of ventricular assist was 2380 days for the A motor and 4120 days for the B motor.

Table 5. Outcomes of subjects (European clinical study: as of June 15, 2007)

Outcome	Value
Mean period of ventricular assist (day)	197 ± 172 (range: 17-711)
Cumulative period of ventricular assist (day)	6500
Number of subjects under ventricular assist (N)	13
Of them, number of subjects under ventricular assist for at least 6 months (N)	13
Of them, number of subjects under ventricular assist for at least 1 year (N)	5
Kaplan-Meier survival estimate (%) at 6 months	76.0 [95% CI, 55.1-88.2]
Rate of subjects who received cardiac transplantation (%) excluding 13 subjects still under ventricular assist	65 (13/20)
Mean period from implantation to cardiac transplantation (day)	185 ± 148 (range: 43-497)
Number of patients aged <60 years (N)	18
Survival estimate at 6 months (%)	94.4 [95% CI, 66.6-99.2]
Number of patients aged <65 years (N)	24
Survival estimate at 6 months (%)	81.3 [95% CI, 56.6-92.7]

Patient demographics, study results, and adverse events are compared between the A motor and B motor groups in Tables 6, 7, and 8, respectively. Mean values were analyzed with ANCOVA. The period and number of hospitalization were tested with the Wilcoxon test. New York Heart Association (NYHA) functional classification was analyzed with the Fisher's exact test. Adverse events were categorized, converted into annual incidence, and compared using the Wilcoxon test. Survival rate was analyzed with log-rank test. The comparison between the A motor and B motor groups showed a statistically significant difference in underlying disease (rate of idiopathic cardiomyopathy), pump motor rotational speed, pump motor current, mean alanine aminotransferase (ALT) of all data measured during the follow-up period after implantation, survival rate, and converted incidence of neurological dysfunction.

The A and B motors differ only in the stricter control of [redacted] during the production process, therefore, there is no difference in their product specifications. Hence, the A and B motor groups could be pooled for evaluation.

Table 6. Comparison of patient demographics between A motor and B motor groups (European clinical study)

Item	Sub-class	A motor group (16 subjects)	B motor group (17 subjects)	*P*-value
Demographics	Mean age (year)	55.3	55.0	0.900
	Mean BSA (m^2)	1.84	1.94	0.181
	Proportion of males (%)	81	88	0.656
Underlying disease	Idiopathic (N [rate])	10 (63%)	4 (24%)	0.037
	Ischaemic (N [rate])	4 (25%)	10 (59%)	0.080
	Hypertrophic (N [rate])	2 (13%)	1 (6%)	0.601
Clinical condition	On inotropic agent (N [rate])	16 (100%)	16 (94%)	1.000
	IABP assist (N [rate])	4 (25%)	2 (12%)	0.398
	NYHA functional class IV (N [rate])	16 (100%)	17 (100%)	1.000
Preoperative haemodynamics	CI ($L/min/m^2$)	1.81	1.84	0.815
	LVEF (%)	20.0	20.5	0.663
	BP (mmHg)	71.5	72.3	0.986
	PAP (mmHg)	34.9	33.7	0.921
	LAP/PCWP (mmHg)	23.3	19.9	0.158
	CVP (mmHg)	11.3	8.4	0.112
	PVR ($dynes \cdot sec/cm^5$)	272	258	0.188
	SVR ($dynes \cdot sec/cm^5$)	1302	1346	0.766
Preoperative blood biochemistry	BUN (mg/dL)	40.4	37.3	0.914
	Cre (mg/dL)	1.5	1.5	0.356
	Bil (mg/dL)	1.4	1.3	0.516
	AST (U/L)	43.1	132.1	0.957
	ALT (U/L)	38.4	191.4	0.528

CI: cardiac index, LVEF: left ventricular ejection fraction, BP: blood pressure, PAP: pulmonary arterial pressure, LAP: left atrial pressure, PCWP: pulmonary capillary wedge pressure, CVP: central venous pressure, PVR: pulmonary vascular resistance, SVR: systemic vascular resistance, BUN: blood urea nitrogen, Cre: creatinine, Bil: bilirubin, AST: aspartate aminotransferase

Table 7. Comparison of primary and secondary endpoints between A motor and B motor groups (European clinical study)

Item	Sub-class	A motor group (16 subjects)	B motor group (17 subjects)	*P*-value
Survival rate	Kaplan-Meier estimated survival rate at 13 weeks (%)	62	100	0.006
Safety	Converted incidence of all adverse events (%)	27.30	8.53	0.214
	Converted incidence of serious adverse events (%)	22.98	4.96	0.062
Pump performance*	Pump flow rate (L/min)	4.81	5.36	0.053
	Pump index (L/min/m^2)	2.61	2.77	0.372
	Pump motor rotational speed (rpm)	1597	1701	0.001
	Pump motor current (A)	0.54	0.62	0.002
Clinical chemistry*	BUN (mg/dL)	27.3	28.3	0.943
	Cre (mg/dL)	1.25	1.40	0.690
	Bil (mg/dL)	1.84	1.12	0.627
	AST (U/L)	54.5	53.8	0.885
	ALT (U/L)	22.5	51.6	0.013
Coagulation system*	PT-INR	2.0	2.2	0.200
	aPTT (sec)	52.4	51.7	0.843
NYHA functional classification at 13 weeks	Class I	2	4	
	Class II	5	9	0.656
Discharge	Number of subjects (N [rate])	10 (63%)	15 (88%)	0.118
	Hospitalization period after implantation (day)	51.7	36.9	0.053
Re-hospitalization	Number of subjects (N [rate])	8 (50%)	9 (53%)	1.00
	Mean hospitalization period (day)	23.7	15.4	0.596

*: Mean value of all data measured during the follow-up period after implantation

aPTT: Activated partial thromboplastin time, PT-INR: International normalized ratio (Prothrombin time)

Table 8. Comparison of adverse events between [redacted] motor and [redacted] motor groups (European clinical study)

Adverse event	**Converted incidence of adverse events***				
	All subjects (event/year)	**[redacted] motor** (event/year)		**[redacted] motor** (event/year)	***P*-value**
		All subjects (N = 16)	Deaths in subjects (N = 6) /surviving subjects (N = 10) /*P*-value		
Haemorrhage	0.91	1.13	2.90/0.08/0.637	0.66	0.178
Arrhythmia	1.94	2.43	4.27/1.33/0.598	1.40	0.575
Hepatic insufficiency	0.44	0.91	2.10/0.20/0.637	0.00	0.128
Infections	4.29	6.25	11.70/2.98/0.048	2.30	0.282
Neurological disorder	1.53	2.97	6.63/0.78/0.056	0.16	0.038
Renal failure	1.10	2.16	5.07/0.41/0.393	0.09	0.232
Respiratory failure	0.77	1.30	2.90/0.34/0.637	0.26	0.867
Right heart failure	1.64	2.19	5.00/0.51/0.393	1.06	1.000
Device failure	0.46	0.95	0.00/1.53/0.258	0.00	0.128
Others	4.81	6.99	15.21/2.06/0.002	2.60	0.065
Total	17.86	27.3	55.8/10.2/0.007	8.53	0.214

*: Converted incidence of adverse events = Sum of the number of subject-converted events for each adverse event/number of subjects

Number of subject-converted events = Number of events for a subject who had the event × (365.25/number of days of ventricular assist for the subject)

[Japanese clinical study]

The clinical study in Japan was intended to confirm the safety and efficacy of DuraHeart during the implantation procedure, post-operative control, and home therapy in patients with end-stage severe heart failure. The study was performed in 6 subjects at 5 Japanese medical institutions from April 4, 2008 to April 23, 2009. The product was evaluated from the start of implantation to 26 weeks after the implantation, or if subjects receive cardiac transplantation or withdraw from the treatment, from the start of implantation to 4 weeks after cardiac transplantation/withdrawal. The efficacy endpoints of the study were (1) success of the implantation, (2) survival, (3) NYHA functional classification and QOL evaluation, (4) pump function evaluation, and (5) number of days on circulation assist. The safety endpoints of the study were (1) adverse events and malfunctions and (2) changes in vital signs and laboratory test values. Study institutions were allowed to discharge subjects and start home therapy when they recovered enough through rehabilitation and could lead a normal daily life. Subjects were trained based on the return-to-home program and confirmed to meet the discharge requirements by the investigator or subinvestigator before discharge. The return-to-home program that included the following items was designed by discussion at each study institution: (1) organization of a hospital medical team responsible for the management of the ventricular assist device, (2) training system for subjects and their caregivers, (3) procedures for preparing for discharge, including the requirements for the living environment, (4) establishment of actions to be taken by the subject, caregiver, and hospital staff in case of emergency at home and system for requesting assistance to related organizations (including the fire department), (5) procedures for monitoring the subject and device at home, and (6) device maintenance and inspection procedures.

For demographics of the 6 subjects, the mean age of the 6 subjects was 45 ± 9 years (29-55 years) and BSA was 1.69 ± 0.16 m^2 (1.46-1.91 m^2). They consisted of 5 male and 1 female subjects. Their primary diseases were dilated cardiomyopathy in 4 subjects, hypertrophic cardiomyopathy in the dilated phase in 1 subject, and ischemic heart disease in 1 subject. The following results were obtained for the efficacy endpoints. (1) The product was successfully implanted in all the subjects. (2) All the 6 subjects survived up to 26 weeks after implantation, with no death observed throughout the evaluation period. Five of the 6 subjects were discharged and started home therapy up to 26 weeks after implantation, although 1 subject of them was re-hospitalized for 11 days due to the poor control of anticoagulant therapy (decreased PT-INR possibly due to dietary effect). (3) QOL evaluated using specific activity scale (SAS) and MOS Short-Form 36-Item Health Survey (SF-36) improved. Cardiac function evaluated by the NYHA functional classification improved for 3 subjects each in Classes IV and III at enrollment, to 5 subjects in Class I and 1 subject in Class II at 26 weeks. (4) The mean pump flow rate remained stable during the evaluation period from the procedure to 26 weeks, as demonstrated by the following results: the mean pump flow rate was 4.3 ± 1.0 L/min (3.1-6.0 L/min) on Day 1 after implantation and 3.8 ± 0.4 L/min (3.4-4.4 L/min) at 26 weeks and the mean pump index was 2.55 ± 0.48 L/min/m^2 (1.82-3.14 L/min/m^2) and 2.28 ± 0.22 L/min/m^2 (1.91-2.56 L/min/m^2), respectively. (5) The number of days on ventricular assist from the implantation procedure to 26 weeks was 181 ± 8 days. The number of days of hospitalization after implantation was 82 ± 53 days. The number of days at home was 99 ± 50 days. The cumulative number of days on ventricular assist was 1083 days. The period from the implantation procedure to discharge in the 5 discharged subjects was 58 ± 6 days. All the 6 subjects received the return-to-home program, during which it was confirmed that the product was compatible with their living environment. The product caused no problem during the home therapy. One subject was not discharged, but hospitalized for a longer period for personal reasons (change of the house to which the subject was scheduled to return). The subject was discharged after the final observation at 26 weeks.

For safety, observed adverse events are listed in Table 9. Comparing adverse events during hospitalization and home therapy showed that adverse events during hospitalization tended to be related to the implantation procedure and included events specific to the product, such as the pain at the pump implantation and infection at the cable exit, while those during home therapy included PT-INR decreased and PT-INR and aPTT increased, which were related to anticoagulant therapy. No malfunction or defective operation of the product occurred during the evaluation period from the start of the implantation procedure to 26 weeks. An alarm was sounded when a communication error between the console and controller, self-test error of the controller, power supply error, or controller error was detected. All these errors occurred as a single error due to the false detection by noise disturbance etc., and were not associated with device abnormality. Five technical malfunctions occurred in 3 subjects. Three events were simultaneous disconnection of 2 systems of power supply from the controller in 2 subjects, 1 event was damage to the percutaneous cable (on the control side) in 1 subject and 1 event was fracture of the battery connector in 1 subject. Additional training was given to prevent simultaneous disconnection of 2 systems of power supply. The damage to the percutaneous cable (on the control side) accidentally occurred when the cable fixing tape was removed with the use of scissors. The damage was repaired later. The fracture of the battery connector occurred at the tip of the battery connector when the battery was removed from the charger. The battery was replaced with a new one and the study institution instructed the subject to carefully handle the battery to avoid dropping the battery or giving a shock to the connector connection.

Two subjects had laboratory adverse events associated with anticoagulant therapy. One subject experienced an increased effect of warfarin by the interaction between fluvastatin and warfarin used to treat hypercholesterolaemia, resulting in the increase in PT-INR to 3.0 at 17 weeks after operation. The dose of warfarin was therefore adjusted. The other subject was re-hospitalized since PT-INR decreased to 2.0 or lower due to dietary effects. The dose of warfarin was

adjusted. Although the decrease in PT-INR was considered to be a serious adverse event from the fact that the subject had to be re-hospitalized, the subject was discharged after the dose adjustment of anticoagulant therapy.

Examining hematologic test parameters showed low preoperative red blood cell (RBC) count, haematocrit (Hct), and haemoglobin (Hb) values in 4 of the 6 subjects. Hematologic test values decreased immediately after implantation in all the subjects, but they returned to the reference range by 26 weeks after operation, which may be due to the improved blood circulation by the pump function of the product. White blood cell (WBC) count was transiently increased immediately after operation as an effect of operation and then gradually lowered to the reference range over time in all the subjects. Platelet (PLT) count was decreased and transiently increased possibly due to operation, and then returned to the reference range in all the subjects. AST and ALT, which are hepatic function related test parameters, transiently increased after operation possibly due to the effect of operation and then gradually returned to the reference range. A drug-related temporary increase in AST and ALT was observed in 1 subject. For renal function related parameters, BUN abnormal and Cre abnormal were observed before operation in 2 and 3 subjects, respectively. Renal function parameters transiently increased immediately after operation and then returned to the reference range in almost all the subjects. This indicates the improvement of renal function by increased cardiac output.

Table 9. Adverse events by event terms and causal relationship (Japanese clinical study)

Causal relationship	**Definitely related**		**Probably related**		**Possibly related**		**Unrelated**		**Total**	
Event term	Number of subjects	Number of events	Number of subjects	Number of events	Number of subjects	Number of events	Number of subjects	Number of events	Number of subjects	Number of events
Total	3 (50%)	5	2 (33%)	6	2 (33%)	6	5 (83%)	25	6 (100%)	42
Ventricular tachycardia	0 (0%)	0	1 (17%)	1	0 (0%)	0	0 (0%)	0	1 (17%)	1
Haemopericardium	0 (0%)	0	0 (0%)	0	0 (0%)	0	1 (17%)	1	1 (17%)	1
Gastralgia	0 (0%)	0	0 (0%)	0	1 (17%)	1	0 (0%)	0	1 (17%)	1
Stomach discomfort	0 (0%)	0	0 (0%)	0	0 (0%)	0	1 (17%)	3	1 (17%)	3
Diarrhoea	0 (0%)	0	0 (0%)	0	0 (0%)	0	1 (17%)	1	1 (17%)	1
Queasy	0 (0%)	0	0 (0%)	0	0 (0%)	0	1 (17%)	1	1 (17%)	1
Chest tightness	0 (0%)	0	0 (0%)	0	0 (0%)	0	1 (17%)	1	1 (17%)	1
Chest pain	0 (0%)	0	0 (0%)	0	1 (17%)	1	0 (0%)	0	1 (17%)	1
Oedema lower limb	0 (0%)	0	0 (0%)	0	0 (0%)	0	2 (33%)	2	2 (33%)	2
Hepatic function disorder	0 (0%)	0	0 (0%)	0	0 (0%)	0	1 (17%)	1	1 (17%)	1
Common cold	0 (0%)	0	0 (0%)	0	0 (0%)	0	1 (17%)	1	1 (17%)	1
Cystitis	0 (0%)	0	0 (0%)	0	0 (0%)	0	1 (17%)	1	1 (17%)	1
Postoperative haemorrhage	0 (0%)	0	0 (0%)	0	0 (0%)	0	1 (17%)	1	1 (17%)	1
Post procedural swelling	0 (0%)	0	0 (0%)	0	0 (0%)	0	1 (17%)	1	1 (17%)	1
Postoperative pain	0 (0%)	0	0 (0%)	0	0 (0%)	0	1 (17%)	1	1 (17%)	1
CPK increased	0 (0%)	0	0 (0%)	0	0 (0%)	0	1 (17%)	1	1 (17%)	1
Blood potassium increased	0 (0%)	0	0 (0%)	0	0 (0%)	0	1 (17%)	1	1 (17%)	1
Hypercholesterolaemia	0 (0%)	0	0 (0%)	0	0 (0%)	0	1 (17%)	1	1 (17%)	1
Dizziness on standing up	0 (0%)	0	0 (0%)	0	2 (33%)	2	0 (0%)	0	2 (33%)	2
Disorientation	0 (0%)	0	0 (0%)	0	0 (0%)	0	1 (17%)	1	1 (17%)	1
Pleural effusion	0 (0%)	0	0 (0%)	0	1 (17%)	1	1 (17%)	1	2 (33%)	2
Pneumothorax (except traumatic pneumothorax)	0 (0%)	0	0 (0%)	0	0 (0%)	0	1 (17%)	1	1 (17%)	1
Epistaxis	0 (0%)	0	0 (0%)	0	0 (0%)	0	1 (17%)	1	1 (17%)	1
Metrorrhagia	0 (0%)	0	0 (0%)	0	1 (17%)	1	0 (0%)	0	1 (17%)	1
Dermatitis contact	0 (0%)	0	1 (17%)	1	0 (0%)	0	1 (17%)	1	2 (33%)	2
Pain at pump implantation	1 (17%)	1	1 (17%)	1	0 (0%)	0	0 (0%)	0	2 (33%)	2
Haemorrhage at cable exit	1 (17%)	1	1 (17%)	1	0 (0%)	0	0 (0%)	0	2 (33%)	2
Pain at cable exit	1 (17%)	1	0 (0%)	0	0 (0%)	0	0 (0%)	0	1 (17%)	1
Sleep disturbance by alarm sound	0 (0%)	0	1 (17%)	2	0 (0%)	0	0 (0%)	0	1 (17%)	2
Infection at cable exit	1 (17%)	1	0 (0%)	0	0 (0%)	0	0 (0%)	0	1 (17%)	1
Granulation at cable exit	1 (17%)	1	0 (0%)	0	0 (0%)	0	0 (0%)	0	1 (17%)	1
PT-INR and aPTT increased	0 (0%)	0	0 (0%)	0	0 (0%)	0	1 (17%)	1	1 (17%)	1
PT-INR decreased	0 (0%)	0	0 (0%)	0	0 (0%)	0	1 (17%)	1	1 (17%)	1

CPK: Creatine kinase

The results of the clinical study intended to confirm the procedure, postoperative management, and compatibility with home therapy in Japan were submitted, with the European clinical study

positioned as a pivotal study. Examining whether the results of the European clinical study could be extrapolated to the Japanese clinical study is important for evaluating the clinical efficacy and safety of the product in Japan. Therefore, the factors which may be the main discrepancies between the European and Japanese studies, including the patient demographics, anticoagulant therapy, and waiting period for cardiac transplantation, were compared as follows. The comparative result showed that the results of the European clinical study could be extrapolated to the Japanese clinical study.

[Comparison of patient demographics between European and Japanese clinical studies]
Comparing the inclusion and exclusion criteria in the European clinical study with "Guidelines for Clinical Evaluation of Next-generation High-function Artificial Heart" (hereinafter called "the guidelines"), attachment 1 to the "Publication of Evaluation Guidelines for Next-generation Medical Devices" (PFSB/ELD/OMDE Notification No. 0404002 from Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated April 4, 2008) showed that the criteria were equivalent to the guidelines, although specific criteria based on numerical values were used in the European study. The inclusion and exclusion criteria in the Japanese study were decided based on those in the European study and guidelines. The patient demographics in the European and Japanese studies are compared in Table 10. The mean age of the European study was higher than that of the Japanese study by approximately ≥10 years. This indicates the difference in the intended age of the patient population undergoing cardiac transplantation between Europe and Japan. The 6-month survival rate was 76% for all the subjects in the European study, but when the results of the 33 subjects in the European study were stratified to examine survival among age groups, there was a tendency of higher survival rate in younger age groups. It should be noted that all the subjects in the Japanese study, whose mean age was 45 ± 9 years (29-55 years), survived at 6 months, while the 6-month survival rate was 94% in the 18 subjects of less than 60 years and 81% in the 24 subjects of 65 years or younger in the European study.

Table 10. Comparison of patient demographics between European and Japanese clinical studies

	European study (N = 33)	**Japanese study** (N = 6)	***P*-value**
Age (year)	55 ± 13	45 ± 9	0.047
Proportion of male subjects	85%	83%	0.660*
BSA (m^2)	1.90 ± 0.19	1.69 ± 0.16	0.017
LVEF (%)	20.2 ± 7.0	20.0 ± 4.6	0.769
LVDd (mm)	75 ± 13	79 ± 19	0.734
CI ($L/min/m^2$)	1.8 ± 0.3	1.8 ± 0.3	0.938
PCWP (mmHg)	22 ± 7	24 ± 9	0.618
CVP (mmHg)	10 ± 5	8 ± 6	0.270
Treatment with inotropic agent (%)	97	100	0.846*

Wilcoxon rank sum test, except for items with *, which was tested with Fisher's exact test (one-sided)
LVDd: Left ventricular end-diastolic diameter

[Comparison of anticoagulant therapy between European and Japanese clinical studies]
The use of appropriate anticoagulant therapy is essential for the management of an implantable ventricular assist device. The anticoagulant therapy used in the European and Japanese clinical studies is outlined in Table 11. The anticoagulant therapy for DuraHeart in the European clinical

study was decided on the reference to clinically established anticoagulant therapy of Novacor and through the interviews with US clinical advisor physicians and discussion at the investigator meetings. It should be noted that the specific numerical values used in the anticoagulant therapy were considered as reference values for managing the therapy during the clinical study and were allowed to be adjusted, depending on patient conditions.

Anticoagulant therapy in the European clinical study was initially started with a recommended PT-INR target value of 2.5 to 3.5. However, based on the management experience of using previous ventricular assist devices at study institutions, excessive anticoagulant therapy was performed, and as a result, haemorrhage-related adverse events occurred in the study. Therefore, the investigators agreed that PT-INR should be controlled to the lowest possible value within the range at the investigator meeting on September 23, 2004, which improved the incidence of haemorrhage related adverse events from 56% (5 of 9 subjects) to 17% (1 of 6 subjects) (the data in the parentheses are based on the interim report as of January 2005).

The recommended PT-INR in the Japanese clinical study was set at 2.0 to 3.0, considering the measured values of PT-INR (2.0-3.0) in the European clinical study and the PT-INR control value of the mechanical valve (2.0-3.0). Anticoagulant therapy was able to be controlled with PT-INR of 2.0 to 3.0 in the Japanese study although small number of subjects were studied. In the Japanese study, haemorrhage-related adverse events occurred, but there were no adverse events leading to thrombus. The same anticoagulant therapy as used in the Japanese study will be recommended in the operating instructions for the Japanese market.

Table 11. Outline of anticoagulant therapy

European clinical study	• All subjects implanted with the investigational device have to receive anticoagulant therapy. • The minimum required anticoagulant therapy includes the following steps: start intravenously administering heparin from 8 to 12 hours after operation to maintain aPTT at 50 to 80 seconds unless marked haemorrhage occurs; and when oral administration becomes possible, administer warfarin to maintain PT-INR at 2.5 to 3.5 and administer 81 mg of aspirin daily (it was agreed during the clinical study that PT-INR should be controlled to the minimum possible value in the above target range). • Additional anticoagulant therapy may be performed based on the best medical judgment of the investigator.
Japanese clinical study	• Start administering heparin (including low molecular weight heparin) to maintain aPTT at 50 to 80 seconds after surgical haemorrhage has been controlled (approximately 8-12 hours after operation). • Start administering warfarin when oral administration becomes possible, unless marked haemorrhage develops. Basically, administer heparin in addition to warfarin until PT-INR exceeds 2.0 to maintain PT-INR between 2.0 and 3.0, and administer 75 to 150 mg of aspirin daily. • Although the use of anticoagulant or antiplatelet drugs other than warfarin and aspirin is not restricted, they should be used carefully only when it is difficult to control coagulation with warfarin and/or aspirin.

[Comparison of waiting period for cardiac transplantation]
The long-term use results of DuraHeart were discussed in consideration of the present situation that the mean waiting period of cardiac transplantation is approximately 2 years in Japan. In the European clinical study, the survival period with the product was ≥1 year in 13 of the 33 subjects (39.4%), ≥2 years in 4 subjects (12.1%), and ≥3 years in 1 subject (3.0%), while it was

≥1 year in 27 of 55 patients (49.1%), ≥2 years in 13 patients (23.6%), ≥3 years in 5 patients (9.1%), and ≥4 years in 1 patient (1.8%) in the European post-marketing surveillance. These results indicate that the accumulated information on the patients with the product may have contributed in the improvement of patient care such as contrivance in controlling anticoagulant therapy, and resulted in an increase in the survival rate. The applicant expects that the product will be also useful in Japan where the waiting period for cardiac transplantation is longer, although it is necessary to accumulate post-marketing data for a long period.

PMDA asked the applicant to explain the following inquiries.

1. For the measures against the event of the temporary stoppage of the pump and subsequent automatic restoration in the [redacted] motor, the applicant explained that the prevention of the malfunction was assured by strictly controlling [redacted] in the [redacted] motor and then confirming [redacted]. Explain the justification of specification, [redacted], used for the measures since the acceptance criteria for distortion are unclear.
2. There was a large difference in the clinical results between subjects with the [redacted] and [redacted] motors in the European clinical study. Discuss the causes of the difference and explain the appropriateness of pooling subjects with the [redacted] and [redacted] motors in one group for evaluation.
3. Explain the differences in patient demographics between Japan and Europe and then discuss the extrapolation of the results of the European clinical study to the Japanese clinical study. Evaluate the clinical results of the product not only from the Japanese clinical study, but also other clinical cases and explain whether the usefulness of the product is acceptable or not, compared to approved implantable ventricular assist devices.
4. Explain the justification of the set BSA for patients for whom the product is indicated.
5. The two systems of power supply were disconnected at the same time in both European and Japanese clinical studies. Explain and justify the measures taken to prevent the event.
6. Explain the training for patients and their caregivers including the measures taken for emergencies outside home.

The applicant responded as follows:

1. [redacted] is strictly controlled [redacted]. Since it is specified that [redacted], the description of specifications in the product specifications will be changed to the description based on the acceptance criteria used in the actual manufacturing process. In addition, the acceptance criteria will be clearly defined by clarifying specific [redacted] to distinguish between [redacted] and [redacted].

Figure 3. Comparison of [redacted] before and after production process improvements

2. A statistically significant difference between the A and B motor groups was observed for the rate of idiopathic causes of heart failure, pump motor rotational speed, pump motor current, mean ALT of all data measured during the post-implantation follow-up period, survival rate, and converted incidence percentage of neurological dysfunction. For above issues, the applicant discussed and explained the justification of the combination of the 2 groups for evaluation.

For the rate of idiopathic causes of heart failure, patients with severe heart failure were included in the candidates for the implantable ventricular assist device regardless of the cause of heart failure since the relationship between the cause of heart failure and clinical results of the ventricular assist has remained unclear. For the pump motor rotational speed, since BSA was larger for the B motor group, the flow rate of the pump may had been set relatively high in the group. The significant difference in the pump motor current resulted from the statistically non-significant, but relatively high BSA, pump flow rate, and pump index in the B motor group. These differences are speculated to result not from the different motors, but from patient demographics. The observed significant difference in the mean ALT of all data during the post-implantation follow-up period resulted not from the different motors, but thought to be from specific clinical chemistry results in specific subjects. The converted incidence of neurological dysfunction was speculated to be attributed by patient demographics such as complications or the effect of slightly excessive anticoagulation control during the early study period.

Age is known to be an independent risk factor for the survival of patients with an implantable ventricular assist device. The mean age of the subjects who died was 64 years and that of the subjects who survived and reached the endpoint was 50 years in the subjects in the A motor group. In the B motor group, all the subjects reached the endpoint of 13 weeks at a mean age of 55 years. The difference in age may had been one of the factors that influenced the survival rate.

The A and B motors are different only in the stricter control of [redacted] in the production process and are not different in the product specifications. In fact, the motor

normally functioned during almost the whole in-use period and caused abnormal operation only when a particularly large load was applied in subjects who had motor [redacted] in the A motor group. Since the A and B motors function in the same manner under all conditions except specific conditions associated with abnormal operation, the applicant determined that there would be no clinical difference in subject safety or data collection.

Based on the above, the applicant considered that combining the A and B motor groups into one group would cause no clinical concerns.

3. There will be no large difference in patient demographics between the Japanese clinical study and post-marketing surveillance since the same criteria are used for selecting patients between the studies. As shown in Table 10, a statistically significant difference in BSA or mean age was observed between the European and Japanese clinical studies. The difference in BSA is considered to reflect the difference in physical constitution between the Europeans and the Japanese. DuraHeart was designed to be implanted even in patients with BSA of as small as 1.1 m^2. The product was also designed to have enough pumping ability for the ventricular assist in patients with BSA of as large as 2.5 m^2. None of the subjects in the European or Japanese clinical study had to cancel the implantation of the product due to small BSA or insufficient pumping power due to large BSA. The applicant therefore considered that the difference in BSA will not directly influence clinical survival rate. For age, it is expected that the mean age of the post-marketing surveillance in Japan, as in the Japanese clinical study, will be lower than that of the European study. Since survival risk increases with age, it is likely that the Japanese study and post-marketing surveillance have higher survival rates than the European study. Therefore, the results of the European study can be extrapolated into the Japanese study.

The results of the Japanese and European clinical studies of DuraHeart and those of Japanese clinical studies of competitors' similar devices are shown in Table 12. Although all the studies were performed in a small number of subjects and discussing patient demographics is therefore difficult, the age of subjects at the time of implantation and BSA were almost identical between the Japanese clinical study of DuraHeart and those of the competitors' devices. The 6-month survival rate was 80% with Novacor and 100% with HeartMate VE, which were at almost the same level as that in the Japanese clinical study of DuraHeart. Although it is difficult to compare adverse events among the studies due to a small number of affected subjects, Novacor, which was the first approved device in Japan, was reported to be associated with adverse events including haemorrhage, thromboembolism accompanied by neurological symptoms, neurological disorder accompanying haemorrhagic tendency, infections, function kidney decreased, and ileus adhesive, while DuraHeart in the present clinical study was associated with the infection at the cable exit, but not with thromboembolism or neurological disorder accompanying haemorrhage. In addition, 5 subjects implanted with DuraHeart were discharged to home during the study and 1 additional subject after the study.

Table 12. Comparison of European clinical study of DuraHeart (subjects aged <60 years) and Japanese clinical studies

	European clinical study of DuraHeart Stratified analysis	**Japanese clinical study of DuraHeart**	**HeartMate VE** [a)]	**NOVACOR** [b)]
Number of subjects	18 (<60 years)	6	5	6 (including 1 subject with off-label use)
Age (year)	46 (29-59)	45 (29-55)	38.6 (21-50)	-
BSA (m^2)	1.94 (1.69-2.40)	1.69 (1.46-1.91)	1.63 (1.50-1.77)	-
Mean number of days with ventricular assist (days)	216 (37-564)	180.5 (173-191)	478 (390-575)	349 (65-1090)
6-month survival rate	94%	100%	100%	4/5
Number of subjects discharged to home	-	5	1	-
Number of subjects undergoing transplantation	10	0	0	-

a) Omoto R, Kyo S, Nishimura M et al. J Artif Organs. 2005;8:34-40

b) Review data on Novacor left ventricular assist system

The data from the European post-marketing surveillance, US clinical study, and Japanese extended clinical study are additionally submitted as the reference data. The European post-marketing surveillance is outlined below. The baseline patient demographics of the study are shown in Table 13. The ventricular assist with DuraHeart was ongoing in 29 of the 55 subjects as of January 15, 2010. The outcomes of all the 55 subjects are summarized in Table 14.

Table 13. Patient demographics
(European post-marketing surveillance: 55 patients, as of January 15, 2010)

Patient demographics	**Mean**	**Standard deviation**	**Minimum value**	**Maximum value**
Age (year)	59	9.7	30	73
BSA (m^2)	2.01	0.21	1.57	2.58
	Number of subjects	**Rate (%)**		
Male	52	95		

Note: Includes 10 subjects from the European clinical study.

Table 14. Outcomes of subjects
(European post-marketing surveillance: 55 patients, as of January 15, 2010)

Mean period of ventricular assist (day)	498 (17-1656)
Cumulative period of ventricular assist (day)	27,376
Number of patients with ongoing assist (N)	29
Number of patients with assist of 6 months or longer (N)	44
Number of patients with assist of 1 year or longer (N)	27
Number of patients with assist of 2 years or longer (N)	13
6-month survival rate (%)	92.4
12-month survival rate (%)	84.3

The US clinical study additionally submitted as the reference data is outlined below. Twenty-eight subjects were enrolled as of February 26, 2010. They included 12 subjects in whom the ventricular assist was ongoing, 10 subjects who underwent cardiac transplantation, deaths in 5 subjects, and 1 subject with device replacement. The outcomes of the 28 subjects are summarized in Table 15.

Table 15. Patient demographics and outcome (US clinical study as of February 26, 2010)

Sex	**Age** (year)	**BSA** (m^2)	**Latest situation/ number of days of using the product**	**Sex**	**Age** (year)	**BSA** (m^2)	**Latest situation/ number of days of using the product**
Male	62	1.86	Transplant/180	Male	37	2.07	Transplant/23
Female	51	1.70	Death/36	Male	59	2.15	Transplant/47
Female	63	1.98	Ongoing/526	Male	66	2.00	Ongoing/44
Female	51	2.18	Ongoing/515	Male	57	2.42	Death/285
Male	43	1.62	Transplant/170	Male	52	2.17	Ongoing/284
Male	70	1.92	Ongoing/401	Male	56	2.47	Death/31
Male	65	2.21	Death/10	Male	56	2.35	Ongoing/234
Male	40	2.36	Transplant/88	Female	47	2.21	Death/13
Male	66	2.25	Transplant/222	Female	57	1.78	Ongoing/99
Male	61	2.12	Transplant/270	Male	62	2.51	Ongoing/99
Male	45	2.02	Ongoing/259	Male	53	2.17	Device replacement/14
Male	67	2.11	Transplant/156	Female	29	1.63	Ongoing/121
Male	58	2.31	Ongoing/179	Male	55	2.61	Ongoing/13
Male	65	2.35	Transplant/151	Mean	54.7	2.25	165.6
Male	38	2.13	Transplant/165				

The summary of the Japanese extended clinical study as of August 31, 2010 were additionally submitted as the reference data and are outlined below. This is a Japanese study which is scheduled to continue from the date of the completion of the Japanese clinical study included in the new medical device application to the marketing approval of DuraHeart in Japan. None of the 6 enrolled subjects died, withdrew from, or dropped out of the study during the evaluation period. All of them were discharged to their home and 2 subjects of them received cardiac transplantation. The ventricular assist in the 6 subjects is summarized in Table 16. Serious adverse events are listed in Table 17. Of observed serious adverse events, those for which a

causal relationship to the product could not be denied are malaise, suspected TIA, and bacteraemia. Malaise was listed because a patient had symptoms suspected of heart failure or autonomic disorder and was hospitalized for close examination. TIA was suspected from clinical symptoms in a subject. The subject was hospitalized due to cerebrovascular disorder suspected from symptoms (numbness in the limbs), but head CT showed no specific lesion, the symptoms were improved over time and the subject was discharged. The causal relationship to the product could not be denied for these 2 events. A patient had bacteraemia due to an infection at the cable penetration site and was hospitalized. The infection was resolved and the subject was discharged. Since methicillin resistant *Staphylococcus aureus* (MRSA) was detected at the cable penetration site after operation, it was considered that the causal relationship to the product could not be denied. These 3 events were not unexpected events since they had been reported in the European clinical study. One serious malfunction was reported. One controller error alarm was issued, followed by one levitation error alarm. Then, the second levitation error alarm was issued, but the event was spontaneously resolved. Subsequently, the same levitation error alarm was again issued at the periodic outpatient visit, and the controller was replaced with a new one as an emergency measure. Since this problem was solved by replacing controllers, a malfunction of the controller was suspected. However, since the cause of the malfunction remains unclear, it is necessary to re-examine the need to take measures against similar controller malfunctions.

Table 16. Summary of ventricular assist
(Japanese extended clinical study as of August 31, 2010)

Item			**Total**
			Number of subjects (%)
Number of subjects examined			6
Cumulative number of days of ventricular assist			3822
Number of days of ventricular assist		Mean ± standard deviation	637 ± 98
		Median value	677
		Minimum to maximum values	437-690
Discharge		No	0 (0)
		Yes	6 (100)
	Number of days before discharge	Mean ± standard deviation	91 ± 80
		Median value	61
		Minimum to maximum values	51-253

Table 17. Serious adverse events (Japanese extended clinical study as of August 31, 2010)

Subject No.	Number of days after operation	Adverse event	Causal relationship to the product as evaluated by investigator (view)
1	318	Cholecystitis acute	Can be denied (probably due to dietary effect)
	481	CRT-D battery depletion, lead failure	Can be denied (CRT-D and lead problem)
	495	Postoperative haemorrhage	Can be denied (within the range of usual postoperative haemorrhage)
2	228	Worsening of periodontal disease	Can be denied (the event developed before implantation)
	282	Loss of consciousness	Can be denied (the event resulted from a mistake in the controller replacement operation)
3	648	Malaise	Cannot be denied
4	468	Suspected TIA	Cannot be denied
5	272	Bacteraemia	Cannot be denied
	282	Ventricular tachycardia	Can be denied (the event was observed before implantation and derived from the underlying disease)
	371	Poor control of anticoagulant therapy	Can be denied (the event was attributable to anticoagulant therapy)
	406	Poor control of anticoagulant therapy	Can be denied (the event was attributable to anticoagulant therapy)

Further, the comparison of survival rate between the INTERMACS database[4] (including Novacor and HeartMate XVE approved in Japan), which is a US post-marketing registry, and the European post-marketing surveillance for DuraHeart, which was submitted as the reference data, is shown in Table 18. It is difficult to directly compare survival rate between the 2 data sources with the inclusion of patients with different age distribution, considering a literature report that the risk of death increases with aging. However, the European post-marketing surveillance had a higher survival rate than patients implanted with existing devices as bridge to transplantation (BTT) in the INTERMACS. The comparison of adverse events is shown in Table 19. Although it is difficult to rigorously compare adverse events because of different surveillance conditions, DuraHeart in the European study had equivalent or lower incidence of adverse events than existing devices. The type of adverse events of DuraHeart was comparable to that observed with the standard use of existing devices as BTT.

Table 18. Comparison of survival rate

	INTERMACS	European post-marketing surveillance (DuraHeart)
3 months	88 (91)*	96.4
6 months	83 (90)*	92.4
12 months	74 (84)*	84.3

* The values in parentheses indicate the survival rate of each device used as BTT.

[4] Second INTERMACS annual report

Table 19. Comparison of adverse events

	INTERMACS	**European post-marketing surveillance (DuraHeart)**
Number of subjects	1092	55
Number of deaths	191	13
Cumulative number of years of ventricular assist*	476	75
Mean number of days of ventricular assist*	159	498
	Incidence Adverse event/100 patient-months	
Device malfunction	1.98	0.56
Haemorrhage	16.52	3.78
Cardiovascular system		
Right heart failure	1.89	0.33
Myocardial infarction	0.07	NA
Arrhythmia	7.68	3.11
Pericardial drainage	1.50	NA
Hypertension	2.31	NA
Arterial thrombus	0.35	0.22
Venous thrombus	1.45	NA
Haemolysis	0.54	NA
Infections	17.46	3.00
Neurological dysfunction	2.87	2.66
Renal failure	2.48	0.44
Hepatic failure	0.91	0.11
Respiratory disorder	4.50	1.22
Wound divulsion	0.47	NA
Mental disorder	1.96	0.11

* Converted from the number and incidence of all adverse events

4. It is speculated that the product is intended to be used for patients with BSA of 1.4 to 2.5 m^2. The lower limit was decided based on the verification with cadavers (implantation was possible in 3 cadavers with BSA of 1.12-1.96 m^2) and reference to BSA in patients included in the European study. The upper limit was calculated from the maximum discharge rate of the product, calculation of cardiac index required for ventricular assist, taking into account the upper limit of Novacor and other devices. However, patients for whom the product is indicated should not be decided only based on the conformance to the recommended BSA. The decision should be made based also on the physician's general judgment, considering the observations of anatomical conditions of the patients. Therefore, it will be stated in the Warnings section of the instructions for use that the suitability for the product should be considered in deciding whether the product can be used or not, and the following statement will be added in the Contraindications section: "Patients considered not suitable for the implantation of DuraHeart by the general judgment of an experienced physician, considering patient's physical constitution, BSA, and anatomical conditions of the intended implantation site."

5. Each power supply connection port of the controller is equipped with a lock mechanism. That is, the connector cannot be removed unless the lock is released. However, disconnection of the power supply itself is an event that could occur by the user's manipulation. Therefore,

healthcare professionals, patients, and caregivers are instructed not to disconnect the 2 power supplies at the same time when replacing the battery in the training program, and the caution has been provided in the operating instructions. When one power supply connector is disconnected from the controller or any trouble occurs in one power supply, the product continues normal operation by the other power supply connector and issues an alarm. If the connectors of the 2 power supplies were disconnected at the same time, the pump will stop, but the product will issue 2 stages of alarms: the product initially issues an alarm of total power loss and then the alarm lamp of the controller blinks in a noticeable manner as compared to the disconnection of 1 power supply and sounds an audible alarm. After the alarm of total power loss is issued, connecting the battery or charger to the controller will immediately activate the auto-start operation as a safety device, which will levitate/rotate the impeller and quickly restart circulation.

Thus, preventive measures against the disconnection of the 2 power supplies at the same time are taken by giving appropriate cautions to healthcare professionals, patients, and caregivers and ensuring safety design. However, since the event occurred in 23 subjects (70 events) in the European study and 2 subjects (3 events) in the Japanese study, the applicant decided that patients would be continuously trained after discharge. Since then, such event has not occurred. The training for patients and caregivers will be continuously provided. At the same time, the event will be considered in future specification changes or development of next-generation products.

6. Medical staff will provide guidance to patients and caregivers according to the return-to-home program before discharge so that they can spend their recuperation time safely by themselves outside the hospital. To assure patient safety and emergency response, patients are prohibited to go out, spend the night out, or receive home therapy at home without caregivers for now. Medical staff will train patients and caregivers on how to handle the product when an emergency alarm is sounded according to the operating instructions. To check proficiency level, the staff will give patients and caregivers practical examinations on power supply control, routine checks, actions in case of alarms, and emergency controller replacement, and repeat the instructions, as required, until they pass all the examination items. Furthermore, medical staff will discuss with patients and caregivers on how to react in case of emergency and decide how to make contact with medical staff. Medical staff will also notify the applicable fire department of the fact that a patient implanted with the product lives in their responsible region and precautions for delivering the patient to hospitals in case of emergency. Patients implanted with the product always carry the patient emergency card provided from their hospitals so that they can immediately make contact with the medical institution in case of emergency. The above "return-to-home" program is essentially the same as that used in Europe where the product has been released. It was confirmed from the Japanese clinical study that the program could be applied to the Japanese medical environment.

Based on the above replies, PMDA concluded as follows:

1. An appropriate decision can be made since the B motor strictly controls [redacted] and then [redacted] as a measure against temporary stoppage of the pump/automatic restoration of the A motor.

2. The A and B motors have the same product specifications and differ only in the stricter control of [redacted]. They are considered different only for a specific condition under which the temporary stoppage of the pump/automatic restoration occurs with the A motor. The subjects in the A and B motor groups were different in some items including survival rate and neurological dysfunction in the European

clinical study. The close analysis of the items showed slight differences in factors expected to influence study results, such as age. Therefore, the differences between the A and B motor groups may be attributable to patient demographics rather than to the difference in the motors. Since such differences result from variations in patients who meet the inclusion criteria, PMDA considered it appropriate to evaluate the product by pooling the results from the 2 groups. Since these analyses revealed that patient demographics influenced the therapeutic results of the product, such as survival rate, this information has to be appropriately provided to medical practices.

3. PMDA's view on the extrapolation of the data from the European study to the Japanese study is as follows: The differences in BSA and mean age between the European and Japanese clinical studies reflect the situations of cardiac transplantation in Europe. It is expected that patients to be implanted with DuraHeart after its marketing approval will not be greatly different in demographics from the subjects in the Japanese clinical study. The differences in BSA and mean age were unlikely to directly influence the study results, considering the BSA and mean age of patients implanted with the product in the 2 studies. It is expected that the product will be used in younger patients and therefore result in higher survival rate in Japan than the European clinical study. Considering these facts, it is difficult to directly extrapolate the results of the European study to the Japanese study, but it would be possible to evaluate the efficacy and safety of the product in Japanese patients based on the European clinical study results.

When the results of the pivotal European clinical study were compared to the INTERMACS database including Novacor and HeartMate XVE, approved in Japan, and any differences were discussed, it was found that usefulness of DuraHeart was not inferior to approved products as an implantable ventricular assist device used for the bridge to cardiac transplantation, although it was not easy to directly compare the data from the 2 sources because of the possible difference in the patient demographics and the definitions of adverse events. Therefore, the clinical efficacy and safety of DuraHeart can be confirmed with the data from the European study.

Since appropriate anticoagulant therapy assures the safe use of DuraHeart, it was considered effective to call attention to its importance in the instructions for use. However, taking account of the possible increase in haemorrhage-related complications by the excessive use of anticoagulant/antiplatelet drugs and the absence of established anticoagulant therapy for implantable ventricular assist devices in Japan and overseas and based on the comments raised in the Expert Discussion, PMDA concluded that providing the operating instructions with the information on the anticoagulant therapy used in the clinical studies is currently the most appropriate action. As for the differences in the medical environment between Japan and foreign countries, the prolonged ventricular assist period before cardiac transplantation due to cardiac transplantation situations in Japan, is a discrepancy that should not be overlooked. It is therefore important to secure the efficacy and safety of the product as used for a long time before introducing it into Japan. The ventricular assist period before cardiac transplantation was 197 ± 172 days (mean ± standard deviation) in the European clinical study, with the longest period being 711 days. The product has been used for at least 1600 days in the European post-marketing surveillance, which is positioned as the reference data. Therefore, the results of the European clinical study are considered to support the ability of the product to withstand the long-term use before cardiac transplantation.

4. Physical constitution of patients is one of the important conditions to be considered before implanting the product since it is related to risks, such as organ perforation, and blood flow required for the product. The lower limit of the recommended BSA was set at 1.4 m^2 based on the verification using cadavers. BSA is one of the criteria for selecting patients suitable for the product, and it should be noted that it is inappropriate to select patients only by BSA. The careful application of the product may be considered for selected patients with BSA of less than

1.4 m^2, when especially required, if an appropriate implantation space is available. On the contrary, it is possible that the product cannot be implanted in patients with BSA of 1.4 m^2 or larger, depending on physical constitution. PMDA therefore considered it appropriate to have the following statement in the Contraindications section of the instructions for use: "Patients considered not suitable for the implantation of DuraHeart by the general judgment of an experienced physician, considering patient's physical constitution, body surface area, and anatomical conditions of the intended implantation site."

5. Disconnecting the 2 power supplies at the same time immediately stops the pump. Power disruption during the ventricular assist with the product is a hazard directly related to patient life support and therefore the occurrence of the event must obviously be avoided. Considering that no similar event has occurred since the continuous training for patients and caregivers was introduced to call attention to the adverse event, it would be an overstatement to say that the current specifications that could lead to the risk of disconnecting the 2 power supplies at the same time is unacceptable as compared to the expected benefits of the product. However, the applicant, as a marketing authorization holder, is obliged to improve the specifications to reduce the risk of power disruption. Therefore, PMDA decided to instruct the applicant to continuously examine measures for reducing the power disruption risk and consider revising the specifications, based on the comments raised in the Expert Discussion.

6. The product is directly related to patient life support and may be used outside medical institutions. Therefore, healthcare professionals, patients, and their caregivers have to be thoroughly trained and a sufficient support system must be established so that appropriate emergency actions can be taken even when patients and their caregivers are outside medical institutions.

In conclusion, the applicant's view that the efficacy and safety of DuraHeart for patients waiting for cardiac transplantation is assured from the European and Japanese clinical study results and other reference data is acceptable. However, because of the small number of subjects in the Japanese clinical study and necessity of securing safety during the long-term assist, the efficacy and safety of the product has to be further secured by collecting post-marketing data from as many patients as possible along with long-term prognosis data. Therefore, PMDA determined that the measure should be required as the condition for approval. The essential points suggested for the safety measures of the product include appropriate anticoagulant/antiplatelet therapy, use of the product only by physicians/medical institutions that have met predetermined standards, and establishment and maintenance of an appropriate training and support system. Since physicians and medical institutions have to fully understand the product to secure efficacy and safety, the following conditions for approval should be imposed: The use of DuraHeart only by physicians and medical institutions that have fully understood the efficacy and safety of DuraHeart and have sufficient knowledge and experience in surgical techniques. Finally, since the product is directly related to patient life support and may be used outside medical institutions, PMDA determined that the following conditions for approval should be imposed: the applicant is required to secure safety by thoroughly training healthcare professionals, patients, and their caregivers and establishing a sufficient support system.

IV. Results of Compliance Assessment by PMDA Concerning the Data Submitted in the New Medical Device Application

[PMDA's conclusion on the results of document-based compliance assessment]

A document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new medical device application. As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the

submitted product application documents.

[PMDA's conclusion on the results of GCP on-site inspection]
A GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new medical device application (H-1-2). As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

[PMDA's conclusion on the results of the QMS document-based and on-site inspection]
A compliance review was conducted in accordance with the provision of paragraph 6 of Article 14 of the Pharmaceutical Affairs Act. As a result, PMDA concluded that there were no particular problems.

V. Overall Evaluation

DuraHeart is an implantable left ventricular assist device intended for improving blood circulation in patients who require cardiac transplantation due to end-stage severe heart failure.

The issues discussed in the regulatory review of DuraHeart were as follows: (1) assurance of the clinical efficacy and safety of the product by the European and Japanese clinical results; (2) appropriate evaluation of malfunctions and adverse events observed during the use of the product to take appropriate post-marketing safety measures; and (3) efficacy and safety of the product during the long-term use.

The PMDA's conclusions, taking account of comments from the Expert Discussion, are as follows:

1. The survival rate at 13 weeks after implantation, which was the primary endpoint of the European clinical study (in 33 subjects), was 81.5% (95% CI, 63.2%-91.2%, Kaplan-Meier test), which met the success criterion based on OPC defined by the published survival data of other implantable ventricular assist devices. The survival rate at 6 months after implantation was 76.0% (95% CI, 55.1%-88.2%, Kaplan-Meier test). It was confirmed that there are no safety problems. The product was successfully implanted in all the 6 subjects of the Japanese clinical study. None of the 6 subjects died during the evaluation period after the procedure. Five of the 6 subjects were discharged to receive home therapy. Their cardiac function and QOL had improved. No particular problems were noted for pump function. Based on these results, PMDA concluded that DuraHeart was not inferior to other approved devices.

2. The essential points for the safe use of the product are appropriate anticoagulant/antiplatelet therapy, use of the product only by physicians/medical institutions that have met predetermined standards, and establishment and maintenance of an appropriate training and support system. Considering the seriousness of the target disease and product characteristics, an implantable ventricular assist device is speculated to inevitably cause adverse events. It is important to take appropriate measures to thromboembolism since its prognosis could be poor when it becomes serious. Although appropriate anticoagulant/antiplatelet therapy is important for thromboembolism, excessive anticoagulant/antiplatelet therapy can increase haemorrhage-related complications. Therefore, appropriate anticoagulant/antiplatelet therapy should be performed at each medical institution with reference to clinical study results. In addition, the appropriate use of anticoagulant/antiplatelet therapy should be described in the instructions for use, and the results of anticoagulant/antiplatelet therapy in clinical studies should be described in the operating instructions to provide information.

A malfunction of the temporary stoppage of the pump/automatic restoration by

[redacted] occurred in the European clinical study. It was resolved by improvement measures taken. An event of the simultaneous disconnection of the 2 power supplies occurred in the European and Japanese clinical studies. It would be an overstatement to say that the current specifications which enable disconnection of the 2 power supplies at the same time is unacceptable as compared to the expected benefits of the product. However, the applicant, as a marketing authorization holder, is obliged to improve the specifications to reduce the risk of power disruption. Therefore, PMDA decided to instruct the applicant to continuously examine the measures for reducing the risk of power disruption and consider revising the specifications.

To ensure the effective and safe use of the product, it is important to appropriately handle any malfunction or adverse event of the product before it becomes serious. Therefore, immediate actions should be taken in case of malfunctions and the product should be used only by physicians and medical institutions that have fully understood the product. Furthermore, patients implanted with the product and their caregivers have to fully understand the product and handle problems encountered during home therapy. Therefore, PMDA determined that the use of the product only by physicians and medical institutions that have fully understood the product was to be included in the conditions for approval (Condition 2).

Since use of the product outside medical institutions is expected, PMDA determined that the full training of healthcare professionals, patients, and their caregivers in the home-therapy program and the establishment of a sufficient support system were to be included in the conditions for approval (Condition 3).

3. Taking account of the current status of cardiac transplantation in Japan, it is concerned that the product will be used for a long time. The product was confirmed to be durable for 2 years in the non-clinical study. The mean assist period before cardiac transplantation in the European clinical study was 197 ± 172 days (mean ± standard deviation), with the longest period being 711 days. The European post-marketing surveillance submitted as the reference data reported a patient in whom the product was used for ≥1600 days. Based on these results, the product is likely to provide efficacy and safety when it is used for a long time. It is expected that the risk of thromboembolism will be reduced by promoting appropriate patient management and providing sufficient information to healthcare professionals and patients. Based on the above, PMDA concluded as follows: Considering that long waiting period is anticipated before cardiac transplantation in Japan, and no implantable ventricular assist device is now available in Japan, the use of the product before cardiac transplantation could increase the possibility of cardiac transplantation in patients with end-stage severe heart failure who could not survive without cardiac transplantation; The condition for approval 1 described below should be imposed, to carefully monitor long-term prognosis since long-term results of the product were limited.

Based on the above issues, PMDA considered that it would be beneficial to offer DuraHeart for medical practice since it was not considered to be inferior to Novacor or HeartMate XVE, which are approved in Japan, in the usefulness as the implantable ventricular assist device used for the bridge to cardiac transplantation. PMDA therefore concluded that the product may be approved after modifying the intended use of the "Intended Use, Indications" in the submitted application form as shown below, with following conditions for approval.

[Intended use]
DuraHeart Left Ventricular Assist System is used to improve the blood circulation until cardiac transplantation is performed in patients who have severe heart failure for which cardiac transplantation is indicated, and show continuous decompensation in spite of drug therapy or circulation assist techniques, such as the use of an external ventricular assist device, and whose

lives cannot be saved without cardiac transplantation.

[Conditions for approval]
The applicant is required to:

1. Perform a use-results survey in all patients including those who completed the extended clinical study in cooperation with related academic societies during the re-examination period. At the same time, observe the long-term prognosis of patients implanted with the assist device and report its analytical results.
2. Establish appropriate qualification criteria for medical institutions and physicians in cooperation with related academic societies, and take appropriate measures to limit the use of this product to physicians and medical institutions who/which understand its efficacy and safety and have sufficient knowledge and experience in surgical techniques, etc.
3. Provide sufficient training for healthcare professionals, patients, and caregivers to ensure the safe and smooth transition to home therapy. The safety of the product should be ensured by establishing a sufficient support system.

DuraHeart Left Ventricular Assist System is a new performance medical device that is classified as a biological product and designated as an orphan medical device. The re-examination period should be 7 years and a use-results survey for all the patients implanted with the product should be performed. In addition, the product should be designated as a specially designated medical device and be tracked since it is assumed that patients implanted with the product will be discharged.

The application should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

[Instructions]
1. Continuously examine the measures for reducing power disruption risk and consider revising the specifications of the product.
2. Continuously collect information, analyze the cause, and take appropriate measures for the disconnection at the magnetic levitation sensor pathway that occurred on September 2, 2010.