October 31, 2013

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]	Jarvik 2000 Implantable Ventricular Assist Device
[Applicant]	Century Medical, Inc.
[Date of application]	January 29, 2010 (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 October 31, 2013 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 not classified as a biological product or a specified biological product.

[Conditions for approval]
The applicant is required to:

1. Establish appropriate qualification criteria for medical institutions and physicians in cooperation with related academic societies, and take necessary measures for the product to be used by physicians who have sufficient knowledge and experience in implantation of ventricular assist devices at qualified medical institutions.

2. Conduct a use-results survey in all patients receiving the product in cooperation with related academic societies, report the results of the long-term outcome analysis to the Pharmaceuticals and Medical Devices Agency, as well as take appropriate measures as necessary.

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

Review Report

October 8, 2013

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]	Jarvik 2000 Implantable Ventricular Assist Device
[Applicant]	Century Medical, Inc.
[Date of application]	January 29, 2010 (Application for marketing approval)
[Items warranting special mention]	Orphan medical devices
[Reviewing office]	Office of Medical Devices I

Review Results

October 8, 2013

[Classification]	Instrument & Apparatus 7 Organ function replacement device
[Generic name]	Implantable ventricular assist device
[Brand name]	Jarvik 2000 Implantable Ventricular Assist Device
[Applicant]	Century Medical, Inc.
[Date of application]	January 29, 2010

[Results of review]
Jarvik 2000 Implantable Ventricular Assist Device (Jarvik 2000) is an implantable ventricular assist device intended for use to improve blood circulation in patients with end-stage severe heart failure who require cardiac transplantation.

The results etc., of studies to support the safety, performance, and efficacy of Jarvik 2000 were submitted as the evaluation data from the nonclinical studies. The data showed no particular problems.

Partial data from the US pivotal clinical study and data from the Japanese clinical study etc., in patients eligible for cardiac transplantation were submitted as the evaluation data from the clinical studies.

Of the patients who were enrolled in the US pivotal clinical study, the study results from 17 subjects implanted with Jarvik 2000 and subjected to GCP inspection were submitted as the evaluation data. The success rate of mechanical circuratory support (MCS) to 180 days after implantation of Jarvik 2000 or to cardiac transplantation, the primary endpoint, was 100% (17 of 17 subjects). However, it should be noted that only the subjects who gave their re-consent to GCP inspection by the Japanese regulatory authority were included in the analyses. Adverse events observed in this study were not substantially different from those reported in association with existing implantable ventricular assist devices in terms of the nature and incidence.

The study results from a total of 24 subjects, including the above 17 subjects, who were enrolled in the US pivotal clinical study and implanted with the product, were submitted as reference data. They were also reviewed together with the evaluation data since evaluating data only from the 17 subjects who were subjected to GCP inspection may lead to an overestimation of the efficacy and safety of Jarvik 2000. According to the study result analysis, the primary endpoint achieved was 91.7% (22 of 24 subjects). Adverse events observed in this study were not substantially different from those reported for existing implantable ventricular assist devices in terms of the nature and incidence.

The study results from a total of 128 subjects who were implanted with the former model of the product fitted with a pin bearing pump in the US pivotal clinical study were also submitted as reference data. The primary endpoint achieved was 64.1% (82 of 128 subjects). There was no statistically significant difference in the incidence of thrombotic adverse events, which was a concern associated with pin bearing pumps, between Jarvik 2000 fitted with a cone bearing pump

and the former model fitted with a pin bearing pump. However, the point estimate of the incidence of such adverse events was lower in Jarvik 2000.

In the Japanese clinical study (6 subjects), the former model fitted with a pin bearing pump was used. The success rate of MCS to 180 days post-implantation, the primary endpoint, was 83.3% (5 of 6 subjects). In the Japanese extended study, conducted as the long-term follow-up of subjects (5 subjects) in whom MCS was successful in the Japanese clinical study, all of the 5 subjects underwent cardiac transplantation with a mean MCS duration of 970 days. Adverse events observed in the Japanese clinical study and its extended study were not substantially different in the nature and incidence from those reported in association with the existing implantable ventricular assist devices.

Jarvik 2000 is powered by a battery, which is connected to a controller. A total of 5 events of power disruption caused by battery replacement errors etc., occurred in the US pilot and pivotal clinical studies. At this point, it seems that the risk of power disruption can be reduced by training. However, the product obviously has a potential risk of disrupting power supply to the pump. Accordingly, the Pharmaceuticals and Medical Devices Agency (PMDA) has determined to instruct the applicant to continue seeking measures to reduce the risk and consider revising the specifications.

PMDA reviewed these results comprehensively based on the discussions in the Expert Discussion and has concluded that the efficacy and safety of Jarvik 2000 are not clearly inferior to those of the existing implantable ventricular assist devices. Given that Jarvik 2000 can be implanted via left thoracotomy, PMDA considered it clinically significant to make it available in clinical practice.

Since Jarvik 2000 should be used by physicians who fully understand the product at qualified medical institutions to ensure its efficacy and safety, PMDA has concluded that a statement to this effect should be included in the conditions for approval.

Considering that no data were available regarding the use-results of Jarvik 2000 in the Japanese clinical study, PMDA has concluded that it is appropriate to impose post-approval requirements as a condition for approval, in which a use-results survey should be conducted in all patients implanted with the product and the long-term outcomes after implantation of the product should be carefully observed.

Since Jarvik 2000 is expected to be used outside medical institutions, PMDA has concluded that it is appropriate to include provision of sufficient training etc., to healthcare professionals, patients, and their caregivers through home-therapy programs and establishment of a sufficient support system in the conditions for approval.

Based on its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that Jarvik 2000 may be approved for the following intended use with the following conditions for approval and that this result should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

[Intended use]
Jarvik 2000 Implantable Ventricular Assist Device is used to improve blood circulation until cardiac transplantation is performed in patients who have severe heart failure eligible for cardiac transplantation, and show continuous decompensation in spite of drug therapy or mechanical

circuratory support, 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. Establish appropriate qualification criteria for medical institutions and physicians in cooperation with related academic societies, and take necessary measures for the product to be used by physicians who have sufficient knowledge and experience in implantation of ventricular assist devices at qualified medical institutions.

2. Conduct a use-results survey in all patients receiving the product in cooperation with related academic societies and report the results of long-term outcome analysis to the Pharmaceuticals and Medical Devices Agency (PMDA), as well as take appropriate measures as necessary.

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

Review Report

October 8, 2013

I. Product for Review

[Classification]	Instrument & Apparatus 7 Organ function replacement device
[Generic name]	Implantable ventricular assist device
[Brand name]	Jarvik 2000 Implantable Ventricular Assist Device
[Applicant]	Century Medical, Inc.
[Date of application]	January 29, 2010 (Application for marketing approval)
[Proposed intended use]	Jarvik 2000 Implantable Ventricular Assist Device (Jarvik 2000) is a complete ventricular bypass system that assists left or right ventricle to maintain circulatory blood flow. Jarvik 2000 is implanted in the body. Jarvik 2000 is intended to be used in patients who require mechanical circulatory support due to weakened heart function etc., while waiting for cardiac transplantation. Jarvik 2000 consists of an implantable ventricular assist device, an external power supply unit and other components. Jarvik 2000 enables patients to stay home until organ transplantation can be performed.
[Items warranting special mention]	Orphan medical devices

II. Product Overview

Jarvik 2000 is an implantable ventricular assist device intended for use to improve blood circulation in patients with end-stage severe heart failure who require cardiac transplantation. The product consists of a blood pump, an outflow artificial blood vessel, an internal cable, a sewing cuff, a protective artificial blood vessel, a controller, an external cable, a portable battery, a reserve battery, a battery cable, a Y cable, a battery charger, and a coring knife (Figures 1-4). The main body of the blood pump is implanted in the left ventricular apex via median sternotomy or left thoracotomy. After connecting the outflow artificial blood vessel to the ascending or descending aorta, blood is removed from the left ventricular apex and sent to the aorta. Jarvik 2000 is the first ventricular assist device in Japan the blood pump of which is inserted into the cardiac cavity. The blood pump is percutaneously-controlled and powered via internal and external cables, and the controller extending from the pump. The blood pump and the controller are powered by the power source (the portable or reserve battery) connected to the controller. Patients need to connect the controller to the portable battery before engaging in daily activities. When patients are immobile and do not change batteries for a certain period of time, such as during sleeping, the system can be powered by the reserve battery connected to the controller.

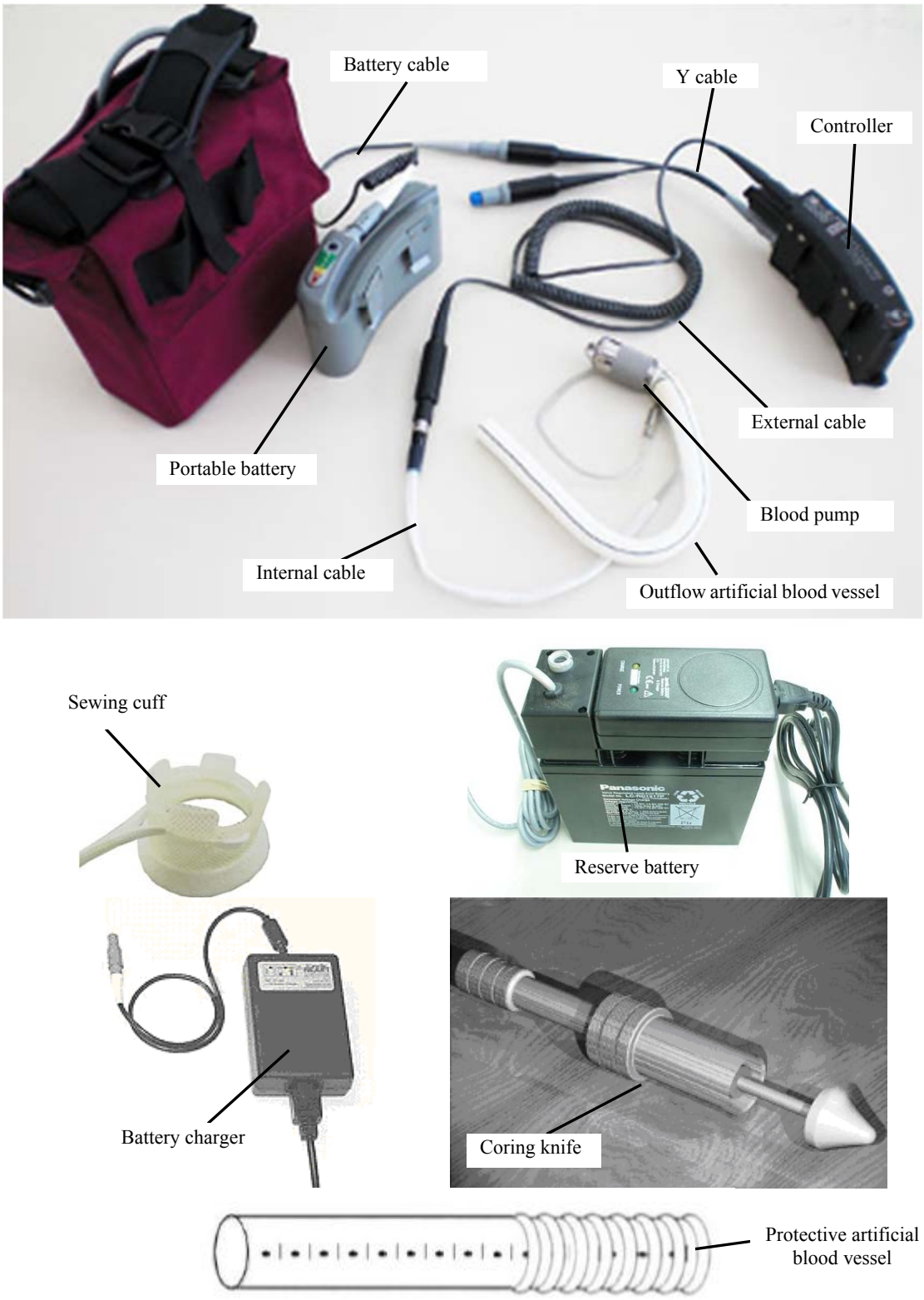

Figure 1. System components

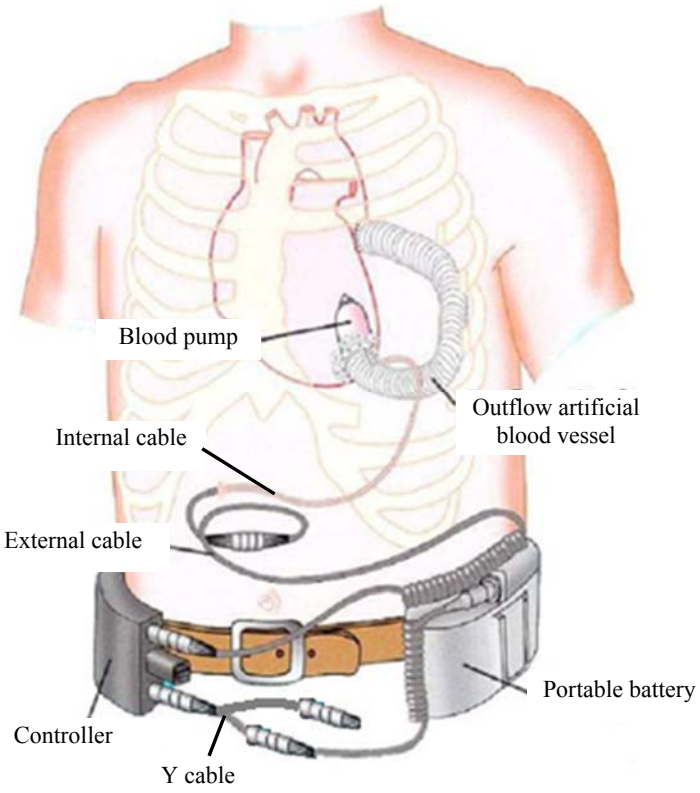

Figure 2. System configuration

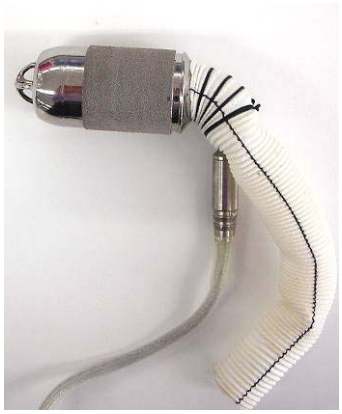

Figure 3. External view of blood pump

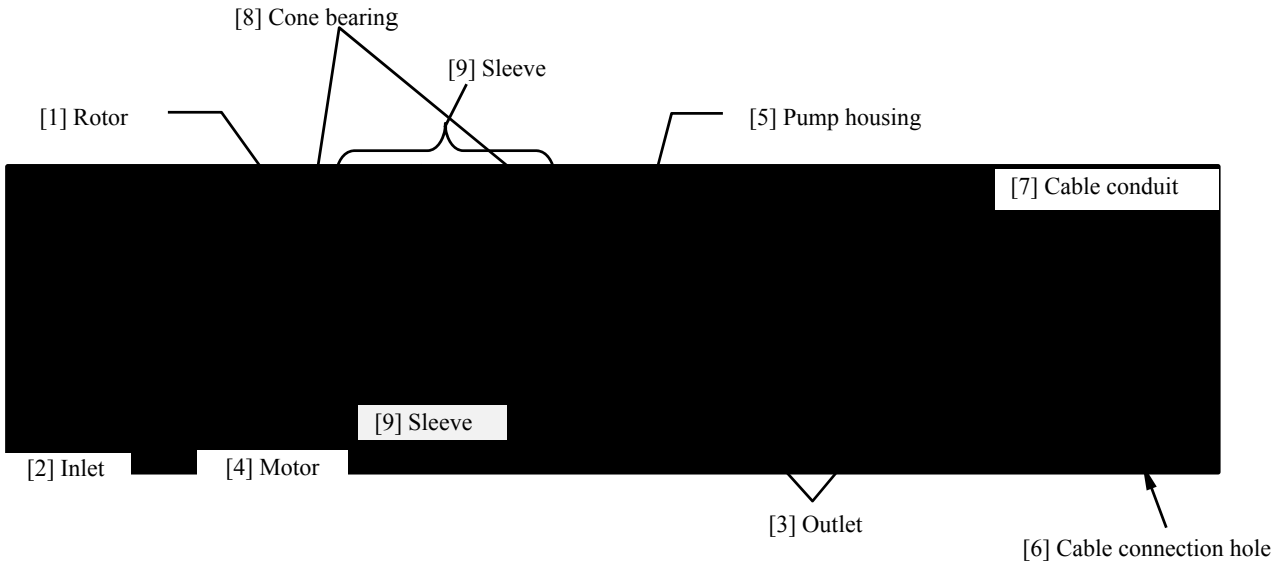

Figure 4. Longitudinal cross-sectional view of blood pump

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 Jarvik 2000 declared that they do not fall under 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.

1.1 Origin or history of discovery

Heart disease is the leading cause of death in the US and the second leading cause in Japan.[1] In particular, heart failure-related mortality is on the increase.[2] The ultimate treatment for end-stage severe heart failure is cardiac transplantation. However, patients have to wait for cardiac transplantation for a relatively long period of time due to the lack of donors even in the US and often die before transplantation because of aggravated conditions. Especially in Japan, extremely few donors are available. For this reason, implantable ventricular assist devices have been developed and used in Japan as well for mechanical circulatory support until cardiac transplantation is performed.

The following 3 types of implantable ventricular assist devices are approved and currently used in Japan: DuraHeart Left Ventricular Assist System (hereinafter referred to as DuraHeart; approval number, 22200BZX00940000); Implantable Ventricular Assist System EVAHEART (hereinafter referred to as EVAHEART; approval number, 22200BZX00939000); and HeartMate II Left Ventricular Assist System (hereinafter referred to as HeartMate II; approval number, 22400BZI00017000). The blood pump of Jarvik 2000 is an axial flow-type[i] as with HeartMate II. Other implantable ventricular assist devices, including HeartMate II, have a structure to remove blood from the left ventricle via a cannula, while the blood pump of Jarvik 2000 is intended to be implanted in the left ventricular apex. Thus the product requires no space in the abdomen to place the pump, which characterizes Jarvik 2000, together with its small weight and volume (Table 1). The approved implantable ventricular assist devices are implanted via median sternotomy, while Jarvik 2000 can be implanted via left thoracotomy. This is another special feature of the product.

Jarvik 2000 Implantable Ventricular Assist Device (hereinafter referred to as Jarvik 2000 VAD, including the devices before and after modifications) was developed in the US. Jarvik 2000 VAD was implanted for the first time in a patient in [redacted] 20[redacted] in the US. The patient successfully underwent cardiac transplantation after being on MCS for [redacted] days. Subsequently, the US pilot study was conducted in 63 subjects at 8 study sites, followed by the US pivotal clinical study.

During the US pivotal clinical study, the following 4 modifications were made to Jarvik 2000 VAD.

(1) Microsphere coating of the pump surface
To prevent thrombus formation in a gap between the outer surface of the pump and the inner wall of the left ventricular myocardium, the surface finishing of the blood pump was changed to microsphere coating, which has been used in other ventricular assist devices.

(2) Addition of intermittent low speed (ILS) function
In the US pivotal clinical study, events of thrombus formation around the aortic valves

[i] A mechanism that sends blood in the direction of the rotational axis of the rotor is called axial flow type, while a mechanism that sends blood in a direction perpendicular to the rotational axis is called centrifugal flow type.

were reported. The increased aortic pressure resulted in less frequent opening and closing of the aortic valves. Blood retention around the aortic valves appeared to cause thrombus formation. Accordingly, to facilitate opening and closing of aortic valves, an ILS function was added to reduce the rotational speed of pump to 7000 rpm for 8 seconds of every 64-second cycle.

(3) Structural change to the internal cable
One case was reported in Japan in which the pump stop alarm was activated, likely caused by an internal cable defect. Five cases of damages to the external part of internal cable were also reported overseas. Accordingly, the cable structure was changed to prevent a short circuit from being caused by extension or flexion of the internal cable.

(4) Structural change to the rotor bearing inside the pump (Figure 5)
The pin bearing pump, in which the rotor inside the pump is supported at 1 point, was associated with a high incidence of thrombotic adverse events. Two subjects in the US pilot study and 6 subjects in the pivotal clinical study underwent pump replacement due to suspected thrombosis. Since thrombosis is most likely caused by blood retention near the pin bearing, the structure of the bearing pump was modified. The newly employed cone bearing pump supports each rotor end inside the pump at 3 points, and this facilitates blood flow to prevent blood from remaining on the sliding surfaces of the rotor and bearing.

Table 1. Comparison with the other implantable ventricular assist devices available in Japan

Marketing authorization holder		Century Medical, Inc.	Thoratec Corporation	Terumo Corporation	Sun Medical Technology Research Corp.
Brand name		Jarvik 2000 Implantable Ventricular Assist Device (Jarvik 2000)	Implantable Ventricular Assist System HeartMate II	DuraHeart Left Ventricular Assist System	Implantable Ventricular Assist System EVAHEART
Approval number		-	22400BZI00017000	22200BZX00940000	22200BZX00939000
Blood pump	Type	Axial flow type, steady-state flow	Axial flow type, steady-state flow	Centrifugal flow type, steady-state flow	Centrifugal flow type, steady-state flow
	Weight	90 g	280 g	540 g	420 g
	Volume	25 mL	114 mL	180 mL	132 mL
	Length	59 mm	-	-	-
	Diameter/height	25 mm	-	45 mm	76 mm
	Maximum flow rate	7 L/min	-	10 L/min	20 L/min
	Pump rotational speed	8000-12,000 rpm	6000-15,000 rpm	1200-2600 rpm	up to 2000 rpm

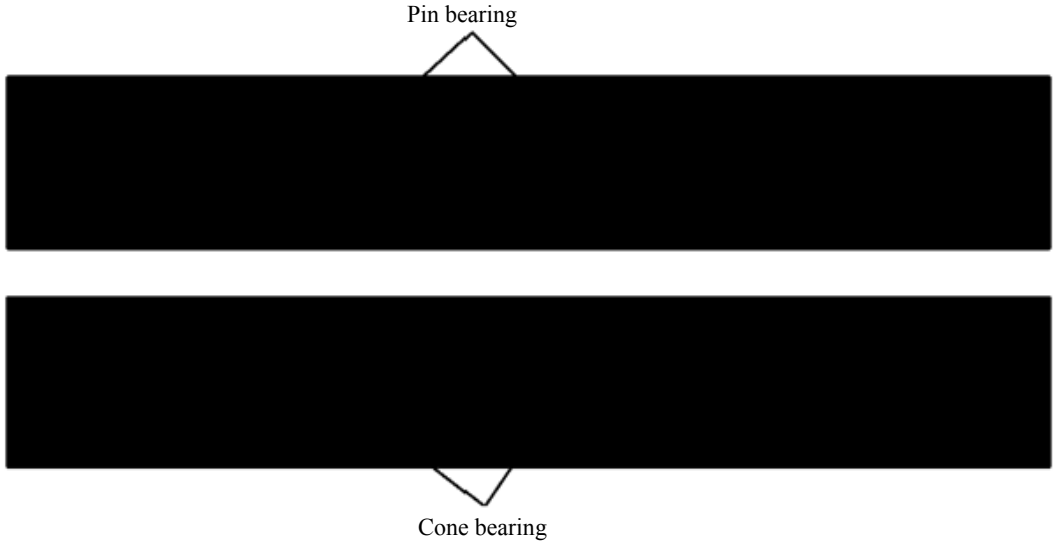

Figure 5. Pin bearing pump (upper) and cone bearing pump (lower)

The Japanese Heart Failure Society, the Japanese Society for Cardiovascular Surgery, the Japanese Association for Thoracic Surgery, and the Japanese Society for Artificial Organs requested the "Study Group on Early Introduction of Medical Devices etc., of High Medical Need" (held by the MHLW) to discuss the Jarvik 2000 VAD. In the third meeting held in June 2007, Jarvik 2000 VAD was selected as a product for which an early approval was to be requested.

Jarvik 2000 VAD was also designated as an orphan medical device in December 2008 (Designation Number [20ki], No. 17) for the following intended use and indications: Jarvik 2000 VAD is intended for bridge-to-transplant use in patients with end-stage severe heart failure almost qualified as cardiac transplant recipients and are under imminent danger of death due to impaired heart function.

1.2 Background of application in Japan

1.2.(1) Background of application

In Japan, a clinical study was conducted using the device to which modifications [see 1.1.(1) Microsphere coating of the pump surface; and (2) Addition of intermittent low speed (ILS) function] were made (pin bearing pump [old model]) from [redacted] 20[redacted] to [redacted] 20[redacted]. Because subject registration was slow in the US pivotal clinical study in patients eligible for cardiac transplantation, the applicant considered whether or not the regulatory submission based on the results of the Japanese and US pilot clinical studies, and results from [redacted] subjects in the ongoing US pivotal clinical study prior to its completion is possible, and requested PMDA's advice (clinical evaluation consultation dated December 25, 2009).

PMDA advised on regulatoy submission and commented that although it was undesirable to file a marketing application in the middle of a pivotal clinical study, PMDA would not refuse to accept the application for Jarvik 2000 VAD if all required conditions are met, including its clinical efficacy and safety, considering the situation in Japan that no implantable ventricular assist device was available at the time of the face-to-face consultation and that Jarvik 2000 VAD had been designated as an orphan medical device. Based on this advice, the applicant filed a marketing application for Jarvik 2000 VAD with a pin bearing pump (old model).

1.2.(2) Proposed intended use

The intended use and indications of Jarvik 2000 VAD when designated as an orphan medical device were "bridge-to-transplant use in patients with end-stage severe heart failure almost qualified as cardiac transplant recipients and are under imminent danger of death due to impaired heart function"[see 1. Origin or history of discovery]. However, the proposed intended use at the time of regulatory submission was as follows: Jarvik 2000 is a complete ventricular bypass system that assists left or right ventricle to maintain circulatory blood flow; Jarvik 2000 is implanted in the body; Jarvik 2000 is intended to be used in patients who require mechanical circulatory support due to weakened heart function etc., while waiting for cardiac transplantation; Jarvik 2000 consists of an implantable ventricular assist device, an external power supply unit, etc.; Jarvik 2000 enables patients to stay home until organ transplantation can be performed.

PMDA asked for the applicant's view on the target patient population since they might be different from those when the product was designated as an orphan medical device.

The applicant responded that the target patient population for Jarvik 2000 VAD is the same as the patient populations of the submitted clinical studies.

PMDA concluded that it would be appropriate to continue reviewing Jarvik 2000 VAD as a medical device intended for bridge-to-transplant use in patients eligible for cardiac transplantation for the following reasons: (a) when designated as an orphan medical device, Jarvik 2000 VAD was originally intended for bridge-to-transplant use in patients with end-stage severe heart failure almost eligible for cardiac transplantation; and (b) all of the submitted clinical studies were conducted to evaluate the clinical efficacy and safety of its use as a bridge to cardiac transplantation in patients eligible for cardiac transplantation.

1.2.(3) Changes to the proposed product after submission

After the application submission, the applicant requested to change the proposed product to the modified model (i.e., Jarvik 2000) [see 1. Origin or history of discovery (1) to (4)] because the post-marketing use results of this modified model in Europe (reference data, MCS for 180 days) were satisfactory.

PMDA, in principle, does not accept changes in shape, structure, etc., of a new medical device submitted, however concluded that the changes above were inevitable since expedited reviews were necessary for patients' benefits and instructed the applicant to submit additional data that support the efficacy and safety of Jarvik 2000. Expedited reviews were considered necessary for the following reasons: the originally proposed product (old model) tended to be associated with an increased risk of thrombus and hemolysis, and result in more frequent pump replacement due to these adverse events than the existing implantable ventricular assist devices; the post-marketing use results in Europe with the current model of the product with a modified structure to minimize thrombus were relatively satisfactory (reference data: the product was implanted in 41 patients between [redacted] 20[redacted] and [redacted], 20[redacted] with a duration of MCS [mean ± standard deviation (SD)] of 165 ± 117 days and survival [Kaplan-Meier test] of 85.6% [95% confidence interval (CI), 77.6%-97.6%] at 1 year post-implantation; 5 deaths occurred); Jarvik 2000 VAD was selected as a product for which an early approval was to be requested by the Study Group on Early Introduction of Medical Devices etc., of High Medical Need; Jarvik 2000 VAD is an orphan medical device designated as a priority review product; and the US pivotal clinical study is ongoing using Jarvik 2000 after it was changed from pin bearing pump based product.

The applicant submitted additional efficacy and safety data, including the results of Jarvik 2000 used in the US pivotal clinical study in patients eligible for cardiac transplantation.

1.3 Usage conditions in foreign countries

Jarvik 2000 VAD received a certification in Europe on April 2005. In Europe, [redacted] units, including units with a pump connected to a postauricular cable (unapplied in Japan), which leads out of the body through the posterior auricle, were shipped by August 2013. The system is not approved in the US (as of October 2013). Table 2 presents malfunctions of Jarvik 2000 VAD resulting in recalls, modifications, or raising cautions.

Since the applicant explained that the events in (a) and from (c) to (g) did not occur often and led to no health hazard, PMDA considered that the applicant's actions including raising cautions to reduce the risk was acceptable at this point. However, for the events whose causes have not been identified, PMDA concluded that it was necessary to collect information via post-marketing surveillance and take further risk reduction measures. PMDA reviewed the additionally submitted data regarding the event (b) and accepted the preventive measures. The additionally submitted data are presented in "3. Stability and durability."

Table 2. Malfunctions in foreign countries (as of September 2013)

Event	Cause	Number of events	Measures
(a) Known or suspected portable battery failure	Likely due to a measurement error of the IC that controlls the LED display of the residual battery level	1	Measures were taken to reset the measurement error of the IC that controlls the LED display of the residual battery level.
(b) Damage to the external part of internal cable	Not identified	11	The inner structure of the internal cable was modified (the modification described in "Origin or history of discovery (3) Structural change in the internal cable").
(c) Damage to the external cable	Not identified	4	The cable was replaced and normal operation of the device thereafter was confirmed. The instructions for use specify cable be replaced once every 6 months.
(d) Lowered volume of the controller alarm	Likely due to the discharged dry-cell batteries of the controller	2	Dry-cell batteries were periodically replaced and the alarm circuit of the controller was modified. The relevant information was provided to medical institutions and measures were taken for attention to be paid to this event thereafter.
	Likely due to the pressure exerted on the alarm speaker by being covered with a hand etc.,	2	Dry-cell batteries were replaced to increase their voltage, and this resolved the lowered volume. Relevant information was provided to medical institutions and measures were taken for attention to be paid to this event thereafter.
(e) Stop alarm activated	Likely due to an instantaneous slow rotational speed of the pump during ILS operation	2	The voltage of the pump motor was fixed, and an alarm trigger was additionally incorporated.
(f) Malfunction of the external device (pump stop alarm activated)	Not identified because it occurred at the patient's home.	1	No health hazard occurred in the patient. The controller and the external cable were replaced. No similar event was reported afterward.
(g) Pump stop alarm not activated	The event did not repeat and its cause could not be identified. The patient reported that the pump stop alarm did not ring when the external cable was removed from the pump. Therefore, the external cable was replaced. After the replacement, the alarm was activated properly.	1	No health hazard occurred in the patient. Attention was to be paid to this event thereafter.
Total		24	

2. Setting of specifications

2.A Summary of the submitted data

The specifications of Jarvik 2000 VAD include correlations between rotational speed, flow rate, and pressure; general requirements for basic safety and essential performance (electrical safety)

(EN60601-1:2001); electromagnetic compatibility (EN55011/3:1991, EN60601-1-2:2001); biological safety (ISO10993-1); ethylene oxide sterilization residuals (ISO 10993-7:1995); a sterility assurance level (SAL) of 10^{-6}; bacterial endotoxins; various alarm functions; external cable tensile strength test; external cable connector tensile strength test; external cable connection/disconnection test; external cable and connector bending test; battery cable tensile strength test; battery cable connection/disconnection test; and battery cable connector tensile strength test. Data justifying these specifications were submitted.

2.B Outline of the review by PMDA

As the configuration of the internal cable was modified after damages to the internal cable were reported, PMDA instructed the applicant to set a specification for the strength of the internal cable.

The applicant responded that the internal cable tensile strength test and internal cable bending test were to be added to the specifications.

As a result of the review on the submitted data, including the performance data, PMDA concluded that the specifications of Jarvik 2000 VAD are adequate as an implantable ventricular assist device and accepted the proposed specifications.

3. Stability and durability

3.A Summary of the submitted data

First, the results of a pump durability test and bearing wear test of pin bearing pumps were submitted as the stability and durability data. The pump durability test of pin bearing pumps showed no failure in any of the 18 pumps for ≥4 years of operation. This demonstrated the reliability of the pumps is beyond the reliability of 80% at a confidence level of 80% for 6 months recommended in the Guidelines for Clinical Evaluation of Next-generation High-function Artificial Heart (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). In the bearing wear test of pin bearing pumps, the wear volume after 3 years of operation was measured. It has been demonstrated that the wear after more than 3 years is not clinically significant. The applicant explained that the pump was shown to be stable for at least 3 years for the following reasons: no abnormality was seen in samples stored for 36 months after sterilization; and no tendency of aging degradation was reported during clinical use as a MCS for at least 7 years.

3.B Outline of the review by PMDA

Since the pin bearing pump was switched to the cone bearing pump, PMDA asked the applicant to submit durability data of cone bearing pumps.

The applicant additionally submitted the results of accelerated pump durability test and pump bearing wear test of cone bearing pumps. The applicant explained that the accelerated pump durability test, in which no failure occurred in any of the 8 pumps during 1-year operation, demonstrated the reliability of the pumps is beyond the reliability of 80% at a confidence level of 80% for 6 months recommended in the Guidelines for Clinical Evaluation of Next-generation High-function Artificial Heart. The applicant also explained that the bearing wear test of cone bearing pumps showed the durability is at least equivalent to that of pin bearing pumps.

PMDA reviewed and accepted the submitted stability and durability data.

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

A declaration of conformity was submitted to declare that Jarvik 2000 VAD 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).

PMDA reviewed the conformity of the product to the Essential Principles and accepted the declaration.

5. Performance

5.1 Physicochemical properties

5.1.A Summary of the submitted data

Data on the physicochemical properties including the test results of bearing pin shear strength were submitted. No problem was indicated in the submitted data. The strength and durability of the internal and external cables and the battery cable are explained in a subsequent section of Mechanical safety.

5.1.B Outline of the review by PMDA

PMDA asked the applicant to explain the strength of the cone bearing.

The applicant explained that the cone bearing pump was considered to be sufficiently strong because it is made of the same material as titanium alloy, and accelerated pump durability test and pump bearing wear test of cone bearing pumps showed durability at least equivalent to that of pin bearing pumps.

PMDA accepted the explanation.

5.2 Electrical safety and electromagnetic compatibility

5.2.A Summary of the submitted data

Electrical safety data were submitted, demonstrating that Jarvik 2000 VAD meets IEC60601-1, the specifications selected for the product.

Electromagnetic compatibility data were submitted, demonstrating that Jarvik 2000 VAD meets EN 55011/3.1991 and EN 60601-1-2, the specifications selected for the product, with the supplement data showing that the product also meets JIS T 0601-1-2.

5.2.B Outline of the review by PMDA

PMDA reviewed and accepted the submitted electrical safety and electromagnetic compatibility data.

5.3. Biological safety

5.3.A Summary of the submitted data

Of the components of proposed Jarvik 2000 VAD, the pin bearing pump, outflow artificial blood vessel, sewing cuff, and part of the internal cable are intended to be in long-term contact with blood, tissues, and mucosa. Other than these components, the coring knife is also expected to be in short-term contact with blood etc., during the implantation procedure. Accordingly, the test results of biological safety of Jarvik 2000 VAD were submitted, the tests of which were conducted with reference to the Reference Material for Basic Principles of Biological Safety Evaluation Test Methods for Biological Safety Evaluation of Medical Devices (Administrative Notice No. 36 from OMDE, ELD, PMSB, MHLW, dated March 19, 2003) and ISO 10993-1. The test results of the hemolytic potential of the pin bearing pump were also submitted, the test of which was based

on ASTM F1841-97:2005 “Standard Practice for Assessment of Hemolysis in Continuous Flow Blood Pumps,” a standard for hemolytic property of blood pumps. The pin bearing pump was tested for cytotoxicity and hemolytic toxicity. The study results were submitted, showing no problem. No study of the outflow artificial blood vessel was performed because its material is the same as that of artificial blood vessel made from synthetic fibers (generic name). The sewing cuff and the internal cable were tested for cytotoxicity, sensitization, genotoxicity, irritation, and implantation. The study results were submitted, showing no problem. The coring knife was tested for cytotoxicity, sensitization, and irritation. The study results were submitted, showing no problem.

5.3.B Outline of the review by PMDA

PMDA asked the applicant to explain the reasons why the following studies were not conducted: (a) biological safety of the cone bearing pump adopted after the application submission and the protective artificial blood vessel added in the course of reviews (the background of its addition is described in “8.B.(3) Use of protective artificial blood vessel”); (b) hemolytic property of the cone bearing pump; (c) sensitization, irritation, pyrogen, acute systemic toxicity, sub-acute toxicity, chronic toxicity, genotoxicity, and local effects after implantation of the pin bearing pump; and (d) acute systemic toxicity, sub-acute toxicity, and chronic toxicity of the sewing cuff and internal cable.

The applicant responded as follows:

(a) The biological safety of cone bearing pumps can be evaluated based on the study results of pin bearing pumps because cone bearing pumps are made of the same material as that of pin bearing pumps. For the newly added protective artificial blood vessel, no new study is necessary since it is made of the same material as that of artificial blood vessels for central circulation system (generic name).

(b) A hemolysis study of cone bearing pumps was additionally conducted. Free hemoglobin concentrations were lower with cone bearing pumps than with pin bearing pumps, which was considered to demonstrate that the risk of hemolysis with the cone bearing pumps is lower than with pin bearing pumps under the conditions of this study.

(c) No new study is considered necessary for the pin bearing pump since it is mainly made of titanium alloy, which is widely used in long-term implantable medical devices. For epoxy resin (another material used in pin bearing pumps), studies other than cytotoxicity and hemolytic toxicity studies for identification were omitted, because it has been used under comparable conditions in other medical devices and it does not come in direct contact with surrounding tissues. For silicon carbide, studies other than cytotoxicity and hemolytic toxicity studies were omitted, since the physicochemical properties of its raw material are very stable against heat, acid-base, and organic solvents and it has been used in the approved implantable ventricular assist devices. These cytotoxicity and hemolytic toxicity studies showed no particularly problematic findings. A preclinical study in cows and clinical long-term use in patients revealed no particular biological safety problem compared to the adverse events reported for other implantable ventricular assist devices.

(d) The absence of evidence suggesting any biological safety issue in the implantation study and the other studies is considered to justify the omission of acute systemic toxicity, sub-acute toxicity, and chronic toxicity studies.

PMDA carefully reviewed these explanations and accepted them.

5.4 Mechanical safety

5.4.A Summary of the submitted data

The mechanical safety data were submitted including the results of following tests: drop impact tests of pin bearing pumps and controller; external cable and external cable connector tensile strength tests; external cable connection/disconnection test; external cable and connector bending test; battery cable tensile strength test; battery cable connection/disconnection test; and battery cable connector tensile strength test. The applicant explained that the submitted data justified the mechanical safety of Jarvik 2000 VAD.

5.4.B Outline of the review by PMDA

PMDA asked the applicant to submit data justifying the mechanical safety of the cone bearing pump and of the internal cable that was modified to address the malfunctions reported in clinical studies

The applicant submitted the results of drop impact test of cone bearing pumps, internal cable tensile strength test, and internal cable bending test. The applicant explained that no malfunctions had been reported in the 28 subjects who were using the internal cable after its structural change (the maximum assist period, 281 days).

PMDA instructed the applicant to carefully follow up the mechanical safety via post-marketing surveillance for the following reasons: the modified internal cable had not been used in many patients in actual clinical practice although its mechanical safety was assessed after the structural change; the possibility of a cable disconnection could not be fully ruled out although no malfunctions had been reported to date for the modified product. PMDA decided to accept the applicant's explanations on the condition of careful follow-up mentioned above.

5.5 Tests to support performance

5.5.A Summary of the submitted data

The data to support performance including the results of performance tests of pin bearing pump and controller, and a preclinical study in cows[ii] were submitted. The pump performance tests, including a test to measure the correlations between rotational speed, flow rate, and pressure, and a test to confirm the operation under a pulsatile flow in a simulated circulation system, demonstrated that the pump provided a sufficient flow. The controller performance tests, including a test of controlling the rotational speed by the controller, and a test of the alarm system, demonstrated appropriate operation of the controller. The results of the preclinical study were submitted in which 6 cows were implanted with the product and observed for 8 weeks at maximum. Successful assist for 8 weeks was achieved in 4 cows, excluding 2 cows euthanized at 25 or 28 days after implantation due to infection.

5.5.B Outline of the review by PMDA

Since the pin bearing pump was switched to the cone bearing pump, PMDA asked the applicant to submit the performance data of the cone bearing pump.

The applicant additionally submitted the results of a preclinical study, in which 6 cows were implanted with cone bearing pumps and were observed for 60 to 65 days. The applicant explained that the cone bearing pump was confirmed to be reliable in assisting cardiac function for 60 days for the following reasons: neither deaths nor serious adverse events occurred in any animal during the study period; no pump stoppage due to device-related thrombus or malfunction occurred although pump stoppage events due to disconnection or damage to the battery cable etc., were reported; and the study results showed no abnormal test values of hemocompatibility or

[ii] Simulation of a clinical study

biochemistry during the use of cone bearing pumps. The applicant explained that the performance of the cone bearing pump was considered sufficient since its structure, other than the bearing part, is the same as that of the pin bearing pump and the risk of hemolysis with the cone bearing pump was considered lower than the pin bearing pump, and determined that no additional performance test of the cone bearing pump was necessary. The applicant also explained that no additional controller performance test of the cone bearing pump is necessary since no change was made to the controller.

PMDA asked the applicant to explain the risk for Jarvik 2000 to cause gastrointestinal haemorrhage considering that bloody stool was observed in 3 of 6 animals in the preclinical study in which cone bearing pumps were used.

The applicant responded as follows:
These 6 cows were tested positive for *Clostridium difficile*. This is the primary causative bacteria for diarrhea and enterocolitis. The bloody stool was likely due to *C. difficile* and it was considered unrelated to the cone bearing pump.

As a result of the review on the submitted data on the tests to support performance, along with the results of the other non-clinical studies and of clinical studies, PMDA concluded that (a) the product's performance is qualified as an implantable ventricular assist device and that (b) the product is associated with a low risk of unacceptable problems as an implantable ventricular assist device. However, a causal relationship of bloody stool to Jarvik 2000 is still not fully ruled out and risk analysis of gastrointestinal haemorrhage is necessary based on the results of the clinical studies etc. The risk of gastrointestinal haemorrhage is described in "8. Clinical data."

6. Risk analysis

Documents summarizing the risk management system and the status of its implementation in Jarvik 2000 VAD in reference to ISO 14971 "Application of Risk Management to Medical Devices" were submitted.

PMDA reviewed and accepted the risk analysis data.

7. Manufacturing process

7.1 Manufacturing process, sterilization method, and sterilization validation

7.1.A Summary of the submitted data

Data on the manufacturing process and manufacturing site of Jarvik 2000, and sterilization validation data as sterilization method information were submitted. Data on in-process test parameters, as quality control information on Jarvik 2000, were submitted.

7.1.B Outline of the review by PMDA

PMDA reviewed and accepted the submitted data on the manufacturing process, sterilization method, and sterilization validation.

7.2 Safety of collagen

7.2.A Summary of the submitted dataThe collagen impregnated into the polyester of the outflow artificial blood vessel of Jarvik 2000 is derived from healthy Australian bovine corium. The applicant explained that the animals are controlled according to the animal husbandry standards approved by the Australian government, that slaughter and corium collection follow the meat export regulations, and that the corium is supplied by a licensed export company.

[redacted]

[redacted].

The applicant also explained that the collagen for Jarvik 2000 is treated with lime ([redacted]) and low pH (pH[redacted], treatment duration ≥[redacted] days) to inactivate viruses and the treated material complies with the Standards for Ruminant Animal Derived Materials and the Standards for Animal Derived Materials of the Standards for Biological Ingredients (MHLW Ministerial Announcement No. 210, 2003), and that the safety of the collagen was therefore assured.

7.2.B Outline of the review by PMDA

PMDA concluded that the applicant's view on the safety of the collagen was reasonable and accepted it.

8. Clinical data

At first, the results of the US pilot and pivotal clinical studies, and Study CMI-JHI-01[iii] in Japan (Japanese clinical study) were submitted, which were all conducted in subjects eligible for cardiac transplantation and in which pin bearing pumps (old model) were used. To prepare evaluation data for the application in Japan, an unscheduled interim analysis was performed in the course of the US pivotal clinical study and a report summarizing the interim analysis was submitted.

Subsequently, as described in "1. Origin or history of discovery and usage conditions in foreign countries etc.," the applicant replaced the pin bearing pump with the cone bearing pump mainly to reduce the risk of thrombotic adverse events. Because the post-marketing treatment results with the cone bearing pump in Europe were satisfactory, the applicant made a request to change the proposed pump from the pin bearing pump to the cone bearing pump.

Although changes to the proposed product after submitting the application are not accepted in principle, PMDA concluded that the above change should be accepted for patients' benefits based on the discussions in the Expert Discussion, provided that the results in patients implanted with the currently proposed products with a cone bearing pump were superior to those in patients implanted with the former model of products with a pin bearing pump in the US pivotal clinical study. In this context, PMDA instructed the applicant to submit a report when data from a large enough number of subjects implanted with the proposed products with a cone bearing pump were accumulated to evaluate the efficacy and safety reliably to a certain degree. PMDA concluded that no additional clinical study needed to be performed in Japan if the results of the US pivotal clinical study would enable the efficacy and safety of the cone bearing pump to be evaluated on the following grounds: all the subjects in the Japanese clinical study were implanted with the former model of products with a pin bearing pump; however, it was considered possible to ensure that the entire Jarvik 2000 VAD, including the external devices such as the controller, would be appropriately used and managed in Japan, even in home therapy.

When the number of subjects implanted with a cone bearing pump in the US pivotal clinical study reached 15, the sample size necessary for pivotal studies defined in the "Guidelines for Clinical Evaluation of Next-generation High-function Artificial Heart", the applicant summarized the study results in a report and submitted it.

[iii] Clinical study identification code. Pin bearing pumps were used.

However, medical institutions participating in the US pivotal clinical study refused GCP on-site inspection by PMDA because no description of GCP on-site inspection by regulatory authorities other than the US FDA was provided in the written information used to obtain informed consent from subjects. Consequently, PMDA was not able to perform on-site inspection intended to verify GCP compliance of the US pivotal clinical study.

The applicant attempted to obtain consent from subjects again using additional written information. Considering that some subjects might not provide re-consent, additional subject registration to the US pivotal clinical study was pursued; eventually, 24 subjects were implanted with a cone bearing pump (Jarvik 2000 group), including 17 subjects who provided re-consent (re-consent group). The applicant rearranged the report to include the analysis of study results only in subjects who gave re-consent (17 subjects in the re-consent group). The report of all subjects implanted with a cone bearing pump including those who did not give re-consent (24 subjects in the Jarvik 2000 group) and the report of the study in subjects implanted with a pin bearing pump (130 subjects in the old model group) were submitted as reference data.

8.A Summary of the submitted data

8.A.1 Summary of the US pivotal clinical study (evaluation data, reference data) ([redacted], 20[redacted] [date of the first enrollment] to [redacted], 20[redacted] [data cut-off date; date of obtaining data from the sponsor, Jarvik Heart])

This was a multicenter, open-label, uncontrolled study conducted in the US. This study was intended to evaluate the clinical efficacy and safety of Jarvik 2000 VAD as a bridge to cardiac transplantation in patients with end-stage severe heart failure (UNOS status[iv] 1A, 1B). Allowing for some dropouts, 160 subjects were planned to be enrolled in the study for the target sample size of 150 subjects evaluable for the primary endpoint in the entire study. In the course of the study, the pump etc., were modified; 130 subjects were implanted with a pin bearing pump (old model group), 24 subjects were implanted with Jarvik 2000 (cone bearing pump) (Jarvik 2000 group), and 17 subjects in the Jarvik 2000 group were included in the GCP inspection population (re-consent group).

The primary endpoint of the study was the success rate of MCS at 180 days post-implantation or until cardiac transplantation,[v] the target rate of which was set at 65% with reference to publications regarding other ventricular assist devices[3,4,5,6,7,8] already approved in the US at the time of planning the clinical study. Table 3 shows the results of the study.

[iv] The status in the transplant waiting list by the US United Network for Organ Sharing
[Status 1A (the most urgently(the highest priority)]: Patients admitted to the listing transplantation center hospital and having at least one of the following devices or therapies in place:
(a) Seriously ill patients for whom mechanical circulatory support including at least one of the following is indispensable:
(1) left and/or right ventricular assist device;
(2) total artificial heart;
(3) intra-aortic balloon pump; or
(4) extracorporeal membrane oxygenator (ECMO).
(b) Patients receiving mechanical circulatory support
(c) Patients on artificial ventilation
(d) Patients requiring continuous cardiotonic agent and continuous monitoring of left ventricular ejection power
[Status 1B (urgently next to 1A, the second highest priority)]: Patients requiring mechanical ventricular support or treatment and having at least one of the following:
(1) left and/or right ventricular assist device; or
(2) continuous intravenous infusion of cardiotonic agent
[Status 7]: Patients transiently excluded from the waiting list because of infection or, economic problems, etc.

[v] Success: Survival on MCS

Table 3. Disposition of enrolled patients and results of the primary endpoint

Study	US pivotal clinical study		
	Old model group (reference data)	Jarvik 2000 group (reference data)	Re-consent group (evaluation data)
Pump	Pin bearing pump	Cone bearing pump	
Number of subjects	152 in total		-
	130*	24*	17
Primary endpoint (Success rate)[95% CI]	64.1% (82/128) [55.1%-72.3%]	91.7% (22/24) [86.0%-97.3%]	100% (17/17) [83.8%-100.0%]

* Including 2 subjects in whom pin bearing pumps were replaced with cone bearing pumps

8.A.2 US pivotal clinical study, Re-consent group (cone bearing pump) (evaluation data)

The study results from 17 subjects who were implanted with Jarvik 2000 (cone bearing pump) in the US pivotal clinical study were included in the GCP inspection population. In 2 of the 17 subjects, pin bearing pumps were replaced with cone bearing pumps. It should be noted that only subjects who provided re-consent to Japanese GCP inspection were included in the analyses (no re-consent available from subjects who died, etc.).

The primary endpoint was the success rate of MCS at 180 days post-implantation or until cardiac transplantation, which was achieved in 100% (17 of 17 subjects) (Table 3).

The secondary endpoints included (a) survival at 60 days post-implantation, (b) improvement in New York Heart Association (NYHA) functional classification, (c) Quality of Life (QOL), and (d) neurocognitive function. Of 17 subjects, 4 subjects underwent cardiac transplantation. The survival at 60 days post-implantation was 100% (4 of 4 subjects). The subjects were classified at 180 days post-implantation by the NYHA functional classification as follows: of the 14 subjects who were Class IV at baseline, 4 were Class I, 5 were Class II, and 1 was Class III; of the 3 subjects who were Class III at baseline, 2 were Class I. Data in 3 subjects at 180 days post-implantation are missing. QOL was measured using the Minnesota Living with Heart Failure Questionnaire (MLHFQ). The score (mean ± SD) was 86.7 ± 14.3 (12 subjects) at baseline and 46.5 ± 25.5 (10 subjects) at 180 days post-implantation. Neurocognitive function was assessed using National Institute of Health (NIH) Stroke Scale. The score (mean ± SD) was 0.40 ± 0.74 (15 subjects) before implantation and 0.09 ± 0.30 (11 subjects) at 180 days post-implantation.

No death was reported. Serious adverse events listed in Table 4 occurred.

Table 4. Serious adverse events (among 17 subjects in the re-consent group) (adverse events reported for the old model in parentheses)

	Device-related/cause-unspecified serious adverse events (related)			Device-unrelated serious adverse events (unrelated)		
	Number of subjects	Incidence	Total number of events	Number of subjects	Incidence	Total number of events
Excessive haemorrhage	0	0.0%	0	2 (1*)	11.8%	3 (1)
Haemolysis	1 (1)	5.9%	1 (1)	0	0.0%	0
Thrombus in device	1 (1)	5.9%	1 (1)	0	0.0%	0
Thromboembolism (non-central nervous system)	0	0.0%	0	0	0.0%	0
Stroke	1	5.9%	1	0	0.0%	0
Transient ischaemic attack	1	5.9%	2	1	5.9%	1
Infections	0	0.0%	0	8 (2)	47.1%	11 (3)
Cardiovascular dysfunction	0	0.0%	0	0	0.0%	0
Right heart failure	0	0.0%	0	0	0.0%	0
Hepatic impairment	1 (1)	5.9%	1 (1)	1 (1)	5.9%	1 (1)
Renal impairment	1 (1)	5.9%	1 (1)	0	0.0%	0
Gastrointestinal malfunction	0	0.0%	0	0	0.0%	0
Pulmonary function impairment	0	0.0%	0	2	11.8%	4
Reoperation	0	0.0%	0	1	5.9%	2
Reoperation due to haemorrhage	0	0.0%	0	3	17.6%	7
Other surgical treatment	0	0.0%	0	3	17.6%	3
Failure of the implanted device	0	0.0%	0	0	0.0%	0
External device failure	3 (1)	17.6%	3	0	0.0%	0
Other adverse events	1 (1)	5.9%	4 (4)	12 (1*)	70.6%	34 (4)
Other neurological dysfunction	0	0.0%	0	1	5.9%	1
Coagulation disorder	0	0.0%	0	0	0.0%	0
Procedure-related failure	1	5.9%	1	0	0.0%	0
Neurocognitive disorder	0	0.0%	0	0	0.0%	0
Air embolism	0	0.0%	0	0	0.0%	0

* The events occurred in the same subject both on MCS with the pin bearing pump and on MCS with the cone bearing pump.

8.A.3 US pivotal clinical study, Jarvik 2000 group (cone bearing pump) (reference data)

The study results are from 24 subjects who were implanted with Jarvik 2000 (cone bearing pump) in the US pivotal clinical study. In 2 of the 24 subjects, pin bearing pumps were replaced with cone bearing pumps.

The primary endpoint achieved was 91.7% (22 of 24 subjects) (Table 3).

The secondary endpoints included (a) survival at 60 days post-implantation, (b) improvement in NYHA functional classification, (c) QOL, and (d) neurocognitive function. Of 24 subjects, 4 subjects underwent cardiac transplantation. The survival at 60 days post-implantation was 100% (6 of 6 subjects). The subjects were classified at 180 days post-implantation by NYHA functional classification as follows: of 15 subjects who were Class IV at baseline, 6 were Class I, 5 were Class II, 1 was Class III, and 1 was Class IV; of 3 subjects who were Class III at baseline, 2 were Class I. Data in 6 subjects at baseline and data in 3 subjects at 180 days post-implantation are missing. QOL was measured using the MLHFQ. The score (mean ± SD) was 86.7 ± 14.3 (12 subjects) at baseline and 46.5 ± 25.5 (10 subjects) at 180 days post-implantation. Neurocognitive

function was assessed using the NIH Stroke Scale, etc. The score (mean ± SD) was 0.40 ± 0.74 (15 subjects) before implantation and 0.09 ± 0.30 (11 subjects) at 180 days post-implantation.

Two deaths were reported and are summarized in Table 5. Serious adverse events listed in Table 6 occurred.

Table 5. Cause of death (Jarvik 2000 group)

Subject ID code	Date of implantation	Duration of MCS (days)	Cause of death	Autopsy	Reason for not performing an autopsy
[redacted]	20[redacted]	157	Not identified	Not performed	The death occurred during home hospice.
[redacted]	20[redacted]	64	Multi-organ failure, acute right ventricular myocardial infarction, and aortic root thrombus	Partially performed	Only Jarvik 2000 was removed because the family refused an autopsy.

Table 6. Serious adverse events (among 24 subjects in the Jarvik 2000 group) (adverse events reported for the old model in parentheses)

Adverse event	Device-related/cause -unspecified serious adverse events (related)			Device-unrelated serious adverse events (unrelated)		
	Number of subjects	Incidence	Total number of events	Number of subjects	Incidence	Total number of events
Excessive haemorrhage	0	0.0%	0	2 (1*)	8.3%	3 (1)
Haemolysis	1 (1)	4.2%	1 (1)	0	0.0%	0
Thrombus in device	1 (1)	4.2%	1	0	0.0%	0
Thromboembolism (non-central nervous system)	0	0.0%	0	0	0.0%	0
Stroke	4	16.7%	5	0	0.0%	0
Transient ischaemic attack	1	4.2%	2	1	4.2%	1
Infections	3	12.5%	3	9 (2)	37.5%	13 (3)
Cardiovascular dysfunction	1	4.2%	1	0	0.0%	0
Right heart failure	1	4.2%	1	0	0.0%	0
Hepatic impairment	2 (1)	8.3%	2 (1)	1 (1)	4.2%	1 (1)
Renal impairment	1 (1)	4.2%	1	0	0.0%	0
Gastrointestinal malfunction	0	0.0%	0	1	4.2%	1
Pulmonary function impairment	0	0.0%	0	4	16.7%	8
Reoperation (excluding haemorrhage)	0	0.0%	0	1	4.2%	2
Reoperation due to haemorrhage	1	4.2%	1	4	16.7%	8
Other surgical treatment	0	0.0%	0	3	12.5%	3
Failure of the implanted device	0	0.0%	0	0	0.0%	0
External device failure	4 (1)	16.7%	4 (1)	0	0.0%	0
Other adverse events	2 (1)	8.3%	5 (4)	15 (1*)	62.5%	37 (4)
Other neurological dysfunction	1	4.2%	1	1	4.2%	1
Coagulation disorder	0	0.0%	0	0	0.0%	0
Procedure-related failure	1	4.2%	1	0	0.0%	0
Neurocognitive disorder	0	0.0%	0	2	8.3%	3
Air embolism	0	0.0%	0	0	0.0%	0

* The events occurred in the same subject both on MCS with the pin bearing pump and on MCS with the cone bearing pump.

8.A.4 US pivotal clinical study, Old model group (pin bearing pump) (reference data)

The study results from 130 subjects who were implanted with the old model of Jarvik 2000 VAD (pin bearing pump) in the US pivotal clinical study are summarized below. Of them, 2 subjects were excluded from the analysis of the primary endpoint because their pumps were replaced with

cone bearing pumps.

The primary endpoint achieved was 64.1% (82 of 128 subjects) (Table 3).

Forty-one deaths were reported and the details are summarized in Table 7. Table 8 lists serious adverse events. Table 9 shows the incidence of adverse events by ILS function status. Table 10 summarizes the details of cases that led to pump replacement.

Table 7. Cause of death (old model group)

Cause of death	Number (#) of events	Incidence (#/41)
Multi-organ failure	15	36.6%
Cardiac failure	6	14.6%
Cerebral haemorrhage, haemorrhage intracranial	4	9.8%
Sepsis, septic shock	3	7.3%
Respiratory failure	3	7.3%
Coronary heart disease	2	4.9%
Haemorrhagic (cerebral) infarction	2	4.9%
Ischaemic cardiomyopathy	1	2.4%
Stroke (the subject requested treatment discontinuation and died)	1	2.4%
Stroke	1	2.4%
Colitis ischaemic	1	2.4%
Thromboembolism	1	2.4%
Hepatic failure	1	2.4%
Severe coagulation disorder	1	2.4%
Cardiogenic shock	1	2.4%
Brain herniation	1	2.4%
Post-stroke complication	1	2.4%
Anoxic brain damage	1	2.4%
Hepatic impairment	1	2.4%
Mycotic aneurysm ruptured	1	2.4%
Ventricular fibrillation	1	2.4%
Renal failure	1	2.4%
Not identified (cardiac arrest)	1	2.4%
Total	51 (≥ 2 events occurred in some subjects.)	

Table 8. Serious adverse events (among 128 subjects in the old model group)

	Number of subjects	Incidence	Total number of events
Excessive haemorrhage	19	14.6%	19
Haemolysis	20	15.4%	22
Thrombus in device	12	9.2%	13
Thromboembolism (non-central nervous system)	12	9.2%	16
Stroke	29	22.3%	34
Transient ischaemic attack	6	4.6%	6
Other neurological dysfunction	19	14.6%	22
Infections	77	59.2%	191
Cardiovascular dysfunction	10	7.7%	10
Right heart failure	5	3.8%	5
Hepatic impairment	29	22.3%	30
Renal impairment	37	28.5%	42
Gastrointestinal malfunction	13	10.0%	19
Pulmonary function impairment	57	43.8%	84
Reoperation	27	20.8%	40
Requiring other surgical treatment	30	23.1%	50
Failure of the implanted device	3	2.3%	3
External device failure	4	3.1%	4
Other adverse events	103	79.2%	316
Reoperation due to haemorrhage	23	17.7%	30
Unexpected adverse event	0	0.0%	0
Coagulation disorder	8	6.2%	9
Procedure-related failure	3	2.3%	4
Neurocognitive disorder	0	0.0%	0

Table 9. Serious adverse events by ILS function status (device-related)

	Without ILS function (n = 81)			With ILS function (n = 49)			*P*-value Fisher's exact test
	Number of subjects (subjects)	Incidence (%)	Total number of events (events)	Number of subjects (subjects)	Incidence (%)	Total number of events (events)	
Excessive haemorrhage	2	2.5%	2	0	0.0%	0	0.5267
Reoperation due to haemorrhage	6	7.4%	6	2	4.1%	2	1.0000
Reoperation	10	12.3%	12	3	6.1%	4	0.3684
Other surgical treatment	0	0.0%	0	1	2.0%	1	0.3769
Haemolysis	15	18.5%	17	3	6.1%	3	0.0656
Thromboembolism (non-central nervous system)	5	6.2%	7	3	6.1%	4	1.0000
Thrombus in device	7	8.6%	8	5	10.2%	5	0.7635
Stroke	10	12.3%	11	10	20.4%	10	0.2228
Transient ischaemic attack	2	2.5%	2	2	4.1%	2	0.6319
Other neurological dysfunction	0	0.0%	0	4	8.2%	4	0.0187
Cardiovascular dysfunction	1	1.2%	1	1	2.0%	1	1.0000
Right heart failure	1	1.2%	1	0	0.0%	0	1.0000
Hepatic impairment	2	2.5%	2	3	6.1%	3	0.3647
Gastrointestinal malfunction	1	1.2%	1	0	0.0%	0	1.0000
Renal impairment	0	0.0%	0	4	8.2%	4	0.0187
Pulmonary function impairment	3	3.7%	3	0	0.0%	0	0.2900
Failure of the implanted device	1	1.2%	1	2	4.1%	2	0.5562
External device failure	1	1.2%	1	3	6.1%	3	0.1500
Infections	8	9.9%	9	2	4.1%	3	0.3180
Other adverse events	11	13.6%	15	14	28.6%	29	0.0414
Unexpected adverse event	0	0.0%	0	0	0.0%	0	1.0000
Coagulation disorder	0	0.0%	0	0	0.0%	0	1.0000
Procedure-related failure	0	0.0%	0	0	0.0%	0	1.0000
Neurocognitive disorder	0	0.0%	0	0	0.0%	0	1.0000

Table 10. Pump replacement

Subject number	Adverse event	Background of replacement
1	Short circuit of the internal cable (replaced with a pump of the same type	Likely due to poor durability or securing of the cable. The cable has been improved.
2	Aggravated haemolysis, and increased bilirubin, LDH, and BNP levels (replaced with a pump of the same type)	The pump was replaced on Day 121 of implantation. No event leading to pump replacement occurred until cardiac transplantation was performed on Day 327 of implantation. The events was probably due to improper procedures in pump implantation or failures in the anticoagulant therapy.
3	Aggravated haemolysis (replaced with a pump of the same type)	The Clinical Event Monitoring Committee considered that the short outflow artificial blood vessel resulted in haemolysis, which was considered attributable to the operator's mistake.
4	Pump replacement due to thrombus in device (replaced with a different pump from Jarvik's)	INR was controlled in the range from 1.0 to 4.0, generally 2.0 or lower. The cause was likely due to inadequate INR control.
5	Pump replacement due to thrombus in device (replaced with a different pump from Jarvik's)	The cause is unknown because there is no information in the CRF regarding the anticoagulant therapy performed before the event.
6	Pump replacement due to thrombus in device (replaced with a different pump from Jarvik's)	The cause is unknown because there is no information in the CRF regarding the anticoagulant therapy performed before the event.
7	Short circuit of the internal cable (replaced with a pump of the same type)	Likely due to poor durability or securing of the cable. The cable has been improved.
8	Pump replacement due to thrombus in the aorta (replaced with a different pump from Jarvik's)	The cause is unknown because there is no information in the CRF regarding the anticoagulant therapy performed before the event.
9	Pump replacement due to thrombus in device (replaced with a pump of the same type)	The event occurred on Day 4 of implantation. INR was controlled between the range of 1.2 to 1.8 from device implantation to onset of the event. The cause was likely due to inadequate INR control.
10	Short circuit of the internal cable (replaced with a pump of the same type)	The event occurred on Day 62 of implantation. The cause was likely due to poor durability or securing of the cable. The cable has been improved.
11	Short circuit of the internal cable (pump repair)	The event occurred on Day 160 of implantation. The cause was likely due to poor durability or securing of the cable. The cable has been improved.
12	Short circuit of the external part of the internal cable (replaced with a cone bearing pump)	The event occurred on Day 176 of implantation. The cause was likely due to poor durability or securing of the cable. The cable has been improved.
13	Pump replacement due to thrombus in device (replaced with a cone bearing pump)	The pump was removed due to thrombus on Day 123 of implantation and replaced by a cone bearing pump.

8.A.5 Japanese clinical study (evaluation data) ([redacted], 20[redacted] [date of the first enrollment] to [redacted], 20[redacted] [date of the last monitoring of subjects])

This was an open-label, uncontrolled study conducted at 5 centers in Japan. This study was intended to evaluate improvement in survival up to cardiac transplantation and safety by using the old model with a pin bearing pump in patients with severe heart failure eligible for cardiac transplantation (3 study sites with 6 subjects enrolled).

The primary efficacy endpoint of the study was the success rate at 180 days post-implantation of the investigational device or survival at 2 months following cardiac transplantation for subjects who underwent cardiac transplantation within 180 days post-implantation. Excluding 1 subject who died on 82 days post-implantation, 5 subjects were still on MCS at 180 days post-implantation without undergoing cardiac transplantation. The success rate was 83.3% (5 of 6 subjects).

The secondary endpoints in Study CMI-JHI-01 included (a) survival at 3 months post-implantation or survival at 2 months post-transplantation for subjects who underwent cardiac transplantation within 3 months post-implantation, (b) change in QOL, (c) comparison of hemodynamics and echocardiographic results before and after implantation, and (d) improvement in heart failure as assessed using NYHA functional classification. One subject died on 82 days post-implantation and no subject underwent cardiac transplantation, resulting in a survival at 83.3% (5 of 6 subjects). QOL was measured using the MLHFQ. QOL was compared between preoperative baseline and 180 days post-implantation (6 months postoperative). The result of overall evaluation (mean ± SD) was 72.9 ± 10.8 (5 subjects) at the time of informed consent and 32.4 ± 19.8 (5 subjects) at 180 days post-implantation. There was a change of -46.8 ± 28.1 (5 subjects). Duplicated and missing questions were found in the questionnaire during the study. The missing question was No. 16 “making you worry?” However, as this question is not classified as one of physical and emotional factors used for the primary evaluation, these missing data would not affect the mean total score of the physical and emotional factors and the score of each factor could be compared. For this reason, exclusion of this question is unlikely to have a major impact on the results of QOL analysis. Blood pressure (mean ± SD) was 76.8 ± 4.3 mmHg (6 subjects) on admission to ICU and 71.8 ± 6.4 mmHg (4 subjects) at 6 days post-implantation. There was a change of 2.3 ± 11.7 mmHg (4 subjects). The left ventricular ejection fraction rate (mean ± SD) was 20.08 ± 4.90% (6 subjects) at the time when informed consent was obtained and 24.10 ± 2.46% (5 subjects) at 180 days post-implantation (6 months postoperative). The 5 subjects who survived at least 3 months post-implantation was classified by the NYHA functional classification as follows: at baseline (at the time of informed consent), 3 were Class IV and 2 were Class III; at 3 months post-implantation, 2 were Class I and 3 were Class II; at 180 days post-implantation (6 months postoperative), 4 were Class I and 1 was Class II.

The safety of the product was evaluated based on deaths, adverse events, and malfunctions. Table 11 shows the narrative description for the death of 1 subject. A total of 67 adverse events occurred in 6 subjects (Tables 12 and 13). Table 14 shows observed device malfunctions.

Table 11. Narative description for the death

Subject number	Clinical course
1	The subject was implanted with the investigational device (old model) on [redacted], 20[redacted] and discharged from the study site on postoperative day (POD) 58. Since haemolysis was suspected on POD 67 (visit for evaluation at 1 week after discharge), the pump rotational speed was reduced on the following day, POD 68. The subject was hospitalized again on POD 70 for close examination, adjustment of pump rotational speed, and drug treatment. At night on POD 73, body temperature increased to 39°C and also WBC and CRP increased. Contrast-enhanced CT and echocardiography revealed inflammatory findings in the pleura, fascia, muscularis, and subcutaneous area along the drive line. Pyothorax was diagnosed. The affected area was incised, washed with normal saline, and placed with a subcutaneous abscess drain. On POD 75, the subject was in a shock state with aggravated pyothorax, intubated in the CCU, and placed under respiratory management. On POD 76, the subject underwent open thoracotomy debridement. Because a large amount of purulent matter attached to the outer surface of the artificial blood vessel, the PTFE graft with a ring and sheet covering the outflow artificial blood vessel was removed as much as practical. Haemorrhage on the lung surface occurred during division of adhesions adjacent to the descending aorta. Suture hemostasis was performed. After the procedure, haemorrhage was observed in the left lung. Due to aggravated respiratory condition, respiratory assist was started using a percutaneous cardiopulmonary support device (PCPS). Brain death occurred on POD 81 and the subject died on the following day, at [redacted] on 82 days after [redacted] implantation.

Table 12. Number of adverse events by severity

System Organ Class (SOC)[*1]	Preferred Term (PT)[*2]	Number of events	Severity		
			Mild	Moderate	Severe
Blood and lymphatic system disorders	Anaemia	4	3		1
	Haemolysis	16	12	4	
	Haemorrhagic diathesis	2	2		
Cardiac disorders	Arrhythmia	1		1	
	Atrial fibrillation	3	2	1	
	Ventricular tachycardia	1	1		
Ear and labyrinth disorders	Vertigo	1		1	
Gastrointestinal disorders	Constipation	2	2		
	Dental caries	1		1	
General disorders and administration site conditions	Feeling abnormal	2	2		
	Oedema peripheral	2	1	1	
	Application site erosion	4	4		
Infections and infestations	Herpes zoster	1		1	
	Nasopharyngitis	4		4	
	Skin infection	1		1	
	Urinary tract infection	1	1		
	Application site infection	7	2	3	2
Injury, poisoning and procedural complications	Joint dislocation	1	1		
Investigations	Weight increased	1		1	
	White blood cell count increased	1		1	
Nervous system disorders	Cerebral haemorrhage	1		1	
	Dizziness	1		1	
	Sensory disturbance	3	3		
Psychiatric disorder	Adjustment disorder	1	1		
Respiratory, thoracic and mediastinal disorders	Pulmonary haemorrhage	1			1
Skin and subcutaneous tissue disorders	Rash	2	2		
Vascular disorders	Orthostatic hypotension	1		1	
	Haemorrhage	1			1

[*1] Classification of adverse reactions according to Medical Dictionary for Regulatory Activities (MedDRA); System Organ Class
[*2] Classification of adverse reactions according to MedDRA; Preferred Terms

Table 13. Number of adverse events by causal relationship

System Organ Class (SOC)[*1]	Preferred Term (PT)[*2]	Number of events	Causal relationship	
			No	Not ruled out
Blood and lymphatic system disorders	Anaemia	4	1	3
	Haemolysis	16		16
	Haemorrhagic diathesis	2	2	
Cardiac disorders	Arrhythmia	1		1
	Atrial fibrillation	3	1	2
	Ventricular tachycardia	1		1
Ear and labyrinth disorders	Vertigo	1		1
Gastrointestinal disorders	Constipation	2	2	
	Dental caries	1	1	
General disorders and administration site conditions	Feeling abnormal	2		2
	Oedema peripheral	2	2	
	Application site erosion	4	1	3
Infections and infestations	Herpes zoster	1	1	
	Nasopharyngitis	4	4	
	Skin infection	1	1	
	Urinary tract infection	1	1	
	Application site infection	7		7
Injury, poisoning and procedural complications	Joint dislocation	1	1	
Investigations	Weight increased	1	1	
	White blood cell count increased	1		1
Nervous system disorders	Cerebral haemorrhage	1		1
	Dizziness	1	1	
	Sensory disturbance	3	3	
Psychiatric disorder	Adjustment disorder	1	1	
Respiratory, thoracic and mediastinal disorders	Pulmonary haemorrhage	1		1
Skin and subcutaneous tissue disorders	Rash	2	2	
Vascular disorders	Orthostatic hypotension	1	1	
	Haemorrhage	1	1	

Table 14. Device malfunctions

Malfunctions	Number of events until 180 days post-implantation
Suspected portable battery malfunction	1
Portable battery charger failure	1
Total	2

8.A.6 Japanese extended clinical study (reference data)

Of the subjects enrolled in the Japanese clinical study, 5 subjects who were on MCS after the end of the 6-month follow-up period were enrolled in the extended clinical study and continued to be followed up. During the extended clinical study, all of the 5 subjects underwent cardiac transplantation (Table 15). Tables 16 and 17 list adverse events and device malfunctions, respectively, reported in this study. The causes for the malfunctions of the portable battery, the controller alarm etc., were identified. After modifications, these malfunctions has not been reported. For subjects in whom the external part of the internal cable was damaged, pump replacement surgery was conducted because of possible pump stoppage. The affected internal cable was the one before the modification was made. No breakage of the modified internal cable has been reported. Cardiac transplantation was successfully performed after MCS with Jarvik 2000 in Japan as well.

Table 15. Dates of implantation and cardiac transplantation in the Japanese extended clinical study

Subject number	Date of implantation	Date of cardiac transplantation	Duration of MCS (days)
1	[redacted], 20[redacted]	[redacted], 20[redacted]	596
2	[redacted], 20[redacted]	[redacted], 20[redacted]	1193
3	[redacted], 20[redacted]	[redacted], 20[redacted]	988
4	[redacted], 20[redacted]	[redacted], 20[redacted]	1089
5	[redacted], 20[redacted]	[redacted], 20[redacted]	983

Table 16. List of serious adverse events found in the Japanese extended clinical study

Adverse event	Number of subjects	Number of events	Incidence (events/patient-year)
Haemolysis	3	3	0.23
Infections	3	4	0.30
Thrombus in device	1	1	0.08
Stroke	4	8	0.60
Right heart failure	2	2	0.15
Gastrointestinal function impairment	1	1	0.08
Other adverse events	2	6	0.45

Table 17. Summary of device malfunctions found in the Japanese extended clinical study

Malfunction	Number of events	Cause	Measures
Damage to the external part of internal cable	1	Likely due to the breakage of the internal cable	The pump was replaced with a new pump (with the internal cable) that had the modified inner structure of the internal cable.
Insufficiently charged portable battery	19	An error in the electronic circuit that drives the lamp to show the residual battery level	The battery was retrieved when this malfunction occurred to reset the electronic circuit.
Abnormal function of the controller alarm	7	The warning alarm volume became low likely due to the pressure put on the alarm speaker by covering it (by hand, etc.).	Caution against covering the speaker was issued. Batteries were replaced to increase their voltage, and this resolved the low volume. Relevant information was provided to medical institutions and measures were taken to pay attention to the tendency of occurrence in the future.
Battery charger malfunction	7	Mechanical failure of the battery charger	The battery charger was replaced.
Damage to the controller	2	Due to external impact, such as dropping	The controller was replaced.
Disconnection of the external cable	2	Due to external impact, such as being caught in a door	The external cable was replaced. The instructions for use specify possession of a spare external cable and cable replacement once every 6 months.
Partial damage to the connection clip of the controller	1	Due to external impact	This does not affect the operation of the controller itself. The controller is replaced upon request.
Bad connection between the portable battery and the battery cable	1	The connector was forcibly pushed in without properly aligning grooves or was screwed in.	The operation manual specifies that the connector should be inserted by aligning grooves and should not be screwed in.
Difficultly in pressing the display button to show the residual portable battery level	1	Likely due to external impact on the display button to shows the residual battery level	This does not affect the battery function itself. The portable battery is to be replaced upon request.

8.B Outline of the review by PMDA

PMDA reviewed the submitted data package focusing on the following issues.

8.B.1 Efficacy

8.B.1.(1) Justification for the clinical evaluation of Jarvik 2000 based on partial results of the US pivotal clinical study

Jarvik 2000 was originally planned to be evaluated mainly based on the study results with the pin bearing pump (old model), for which an application for approval was originally planned, as the primary evaluation data, and additionally based on the study results with the cone bearing pump (Jarvik 2000 [currently proposed product]), which replaced the pin bearing pump in the course of the application process, in a number of subjects that are enough for confirming non-inferiority of the cone bearing pump to the pin bearing pump. However, the study results in 100 subjects implanted with a pin bearing pump were an unplanned interim analysis. In addition, since GCP on-site inspection by the Japanese regulatory authority could not be performed due to insufficient written information provided in obtaining informed consent from subjects, the results could not be used as the evaluation data. As a result, the interim results in a small number of subjects implanted with a cone bearing pump alone were submitted for regulatory review. PMDA asked the applicant to justify the evaluation of Jarvik 2000 based on the above study results.

The applicant responded as follows:

The pump was improved from pin bearing based to cone bearing based in order to minimize thrombotic adverse events. The improved pump is approximately 4 mm longer and 1 mm thicker than the former pin bearing pump. However, since its external shape or operating principle was not changed, the usefulness of Jarvik 2000 was continued to be evaluated according to the same protocol.

The US pivotal clinical study was originally intended to evaluate Jarvik 2000 VAD in 150 subjects assuming the target success rate of 65% and the lower limit of 95% confidence interval (CI) of 57% with reference to publications regarding other ventricular assist devices approved in the US at the time of planning the clinical study. At the time of data fixation, 152 subjects were included in analyses, of whom 24 subjects were implanted with the cone-shaped bearing pump. Although the data from these 24 subjects are partial results of this clinical study, this sample size meets the requirement for pivotal studies (approximately 15 subjects) recommended in the "Guidelines for Clinical Evaluation of Next-generation High-function Artificial Heart." Of them, 17 subjects gave re-consent to the access by the Japanese regulatory authority to source data for GCP compliance inspection. This sample size also meets the requirement for clinical evaluation recommended in the guidelines. For these reasons, the sample size of 17 was considered sufficient for the evaluation of Jarvik 2000.

PMDA considers that the change of the bearing system, including the other 3 modifications described in "1. Origin or history of discovery" affects the efficacy and safety of Jarvik 2000, and therefore, in principle, an additional study should be newly designed and conducted. However, while many adverse events occurred before the modification, non-clinical studies etc., demonstrated that risk reduction was expected as a result of the changes to the investigational device. Considering this fact, the changes to the investigational device to prevent subjects' study-related injuries should not be denied and the continuation of the study can be justified.

The analysis of only the data from subjects implanted with a cone bearing pump cannot be accepted in principle, and an additional study should have been newly designed and conducted. However, considering that Jarvik 2000 is an orphan medical device, PMDA concluded, with reference to the discussions in the Expert Discussion, that data from these subjects should be

accepted and comprehensively evaluated, together with currently available reference data, if data from a large enough number of subjects were accumulated for the efficacy and safety evaluation of Jarvik 2000.

8.B.1.(2) Efficacy of Jarvik 2000

For this application, the results of subgroup analysis of only the data from 24 subjects implanted with a cone bearing pump were submitted. Of them, 17 subjects gave re-consent to GCP inspection. PMDA asked the applicant to justify using the results of this subgroup analysis to verify the efficacy of Jarvik 2000.

The applicant responded as follows:

The success rate, the primary endpoint, in 152 subjects including 128 implanted with a pin bearing pump and 24 implanted with a cone bearing pump, was 68.4% (104 of 152 subjects, including 48 subjects who survived and 56 subjects who underwent cardiac transplantation) and the lower limit of 95% CI was 60.4%. These exceeded the protocol-specified target success rate of 65% and the lower limit of 95% CI of 57%. Of the 24 subjects implanted with the cone bearing pump, MCS succeeded in 22 (91.7%).

The submitted clinical results were obtained from a large enough number of subjects to meet the sample size defined in the "Guidelines for Clinical Evaluation of Next-generation High-function Artificial Heart." However, although it was impossible to obtain re-consent from dead subjects, the efficacy of Jarvik 2000 may be overestimated when only the data from those who were subjected to GCP inspection and not from dead subjects were included in the analysis. Therefore, the data from those who were not subjected to GCP inspection were also considered necessary to be analyzed, and the analysis was performed by assuming that of the 24 subjects, 7 subjects who were not subjected to GCP inspection had all failed to achieve MCS success. This analysis revealed a success rate of 70.8%, which was not statistically significantly different from the clinical study results of the other ventricular assist devices available in Japan as shown in Table 18.

Table 18. Success rate with each device

	Total number of subjects	Number of subjects with MCS success	Success rate	95% CI	Compared with the cone bearing pump (worst condition)
Cone bearing (worst condition)	24	17	70.8%	-	-
Cone bearing	24 (17)	22 (17)	91.7% (100.0%)	86.0%-97.3%	-
EVAHEART Pivotal clinical study	15	13	86.7%	77.9%-95.4%	$\chi^2 = 1.304$ $P = 0.253$
DuraHeart	33	26	78.8%	71.7%-85.9%	$\chi^2 = 0.474$ $P = 0.490$
HeartMate II	126	89	70.6%	66.6%-74.7%	$\chi^2 = 0.004$ $P = 0.984$

PMDA concluded that the efficacy evaluation of Jarvik 2000 as an implantable ventricular assist device was acceptable for the following reasons: 22 of 24 subjects achieved MCS success; the study results of the cone bearing pump did not indicate that it was clearly inferior to the other ventricular assist devices available in Japan even when all of the subjects who did not provide re-consent were assumed to have failed to achieve MCS success as shown in Table 18.

8.B.2 Safety

8.B.2.(1) Safety of Jarvik 2000 VAD

PMDA reviewed the study results of the originally proposed pin bearing pump (old model) and raised safety concerns compared with the existing implantable ventricular assist devices especially in terms of the incidences of haemolysis, thrombus in device, stroke, reoperation, and pump replacement. Considering the subsequent change in the pump from the old model to the currently proposed pump (cone bearing pump), PMDA asked the applicant to explain (a) the effects of the changes made from the original application on safety and (b) that the safety of the cone bearing pump is satisfactory compared to the other implantable ventricular assist devices available in Japan.

The applicant explained as follows:

(a) Table 19 shows adverse events reported by subjects implanted with the pin bearing pump (old model) and those with the cone bearing pump (Jarvik 2000) in the US pivotal clinical study. The incidence of adverse events with the pin bearing pump was 15.4% (20 of 130 subjects) for haemolysis, 9.2% (12 of 130 subjects) for thrombus in device, and 22.3% (29 of 130 subjects) for stroke. The incidence of adverse events with the cone bearing pump was 4.2% (1 of 24 subjects) for haemolysis, 4.2% (1 of 24 subjects) for thrombus in device, and 16.7% (4 of 24 subjects) for stroke. The 95% CI for the incidence of stroke + transient ischemic attack (TIA) in subjects implanted with the cone bearing pump (N = 24 [N = 17 in the re-consent group]) was 12.5% to 29.1% (4.0%-19.6%). On the other hand, the 95% CI for incidence of haemolysis and thrombus in device was both 0.1% to 8.3% (0.2%-11.6%). Although the differences in the incidences of these adverse events between the 2 types of pumps were not statistically significant, the incidences of adverse events tended to decrease due to the change in pump bearing system.

   Many subjects implanted with the pin bearing pump required pump replacement. As shown in Table 10, the causes for pump replacement were; thrombus in the pump in 5 subjects, cable breakage in 5 subjects, haemolysis in 2 subjects, and thrombus in the aorta in 1 subject. No subject in the Jarvik 2000 group (the cone bearing pump after a structural change of the cable) required pump replacement although the number of subjects in this group was limited.

(b) The results of the cone bearing pump were compared with those of the existing similar devices. The incidence of stroke was 15.2% (5 of 33 subjects, 95% CI [8.9%-21.4%]) for DuraHeart, 46.7% (7 of 15 subjects, 95% CI [34.9%-58.4%]) forr EVAHEART, and 8.7% (11 of 126 subjects, 95% CI [6.2%-11.2%]) for HeartMate II. The incidence of TIA for the devices above was 15.2% (5 of 33 subjects, 95% CI [8.9%-21.4%]), 13.3% (2 of 15 subjects, 95% CI [5.3%-21.3%]), and 7.9% (10 of 126 subjects, 95% CI [5.5%-10.3%]), respectively. The incidence of stoke + TIA for the devices above was 30.3% (10 of 33 subjects, 95% CI [22.3%-38.3%]), 60.0% (9 of 15 subjects, 95% CI [48.5%-71.5%]), and 16.7% (21 of 126 subjects, 95% CI [13.3%-20.0%]), respectively. The incidence of stroke + TIA for EVAHEART was significantly higher than that in the re-consent group (2 of 17 subjects [11.8%]) ($P = 0.028$, Fisher's exact test). None of the existing similar devices were associated with a significantly lower incidence of adverse events than that found in the Jarvik 2000 group (5 of 24 subjects [20.8%]). Haemolysis did not occur in patients receiving DuraHeart and EVAHEART, while 3 cases of haemolysis were reported by patients receiving HeartMate II (2.4%, 95% CI [1.0%-3.7%]).

Based on the results above, the applicant considered that the safety of Jarvik 2000 is acceptable as an implantable ventricular assist device.

Table 19. Comparison of serious adverse events reported for the old model and Jarvik 2000 groups

	Old model group (pin bearing pump) (N = 130*)			Jarvik 2000 group (cone bearing pump) (N = 24 [N = 17]*)			*P*-value Fisher's exact test
	Number of subjects	Incidence	Total number of events	Number of subjects	Incidence	Total number of events	
Excessive haemorrhage	19	14.6%	19	2 (2)	8.3% (11.8%)	3 (3)	0.5324
Haemolysis	20	15.4%	22	1 (1)	4.2% (5.9%)	1 (1)	0.2007
Thrombus in device	12	9.2%	13	1 (1)	4.2% (5.9%)	1 (1)	0.6932
Thromboembolism (non-central nervous system)	12	9.2%	16	0 (0)	0.0% (0.0%)	0 (0)	0.2151
Stroke	29	22.3%	34	4 (1)	16.7% (5.9%)	5 (1)	0.7867
Transient ischaemic attack	6	4.6%	6	2 (2)	8.3% (11.8%)	3 (3)	0.6113
Other neurological dysfunction	19	14.6%	22	2 (1)	8.3% (5.9%)	2 (1)	0.5324
Infections	77	59.2%	191	12 (8)	50.0% (47.1%)	16 (11)	0.5007
Cardiovascular dysfunction	10	7.7%	10	1 (0)	4.2% (0.0%)	1 (0)	1.0000
Right heart failure	5	3.8%	5	1 (0)	4.2% (0.0%)	1 (0)	1.0000
Hepatic impairment	29	22.3%	30	3 (2)	12.5% (11.8%)	3 (2)	0.4123
Renal impairment	37	28.5%	42	1 (1)	4.2% (5.9%)	1 (1)	0.0093
Gastrointestinal malfunction	13	10.0%	19	1 (0)	4.2% (0.0%)	1 (0)	0.6979
Pulmonary function impairment	57	43.8%	84	4 (2)	16.7% (11.8%)	8 (4)	0.0127
Reoperation	27	20.8%	40	1 (1)	4.2% (5.9%)	2 (2)	0.0798
Requiring other surgical treatment	30	23.1%	50	3 (3)	12.5% (17.6%)	3 (3)	0.2929
Failure of the implaned device	4	3.1%	4	0 (0)	0.0% (0.0%)	0	0.0005
External device failure	3	2.3%	3	4 (3)	16.7% (17.6%)	4 (3)	0.0118
Other adverse events	103	79.2%	314	15 (12)	62.5% (70.6%)	42 (38)	0.1121
Reoperation due to haemorrhage	23	17.7%	30	5 (3)	20.8% (17.6%)	9 (7)	0.7738
Unexpected adverse event	0	0.0%	0	0 (0)	0.0% (0.0%)	0 (0)	1.0000
Coagulation disorder	8	6.2%	9	0 (0)	0.0% (0.0%)	0 (0)	0.3589
Procedure-related failurer	3	2.3%	4	1 (1)	4.2% (5.9%)	1 (1)	0.4959
Neurocognitive disorder	0	0.0%	0	2 (0)	8.3% (0.0%)	3 (0)	0.0234
Air embolism	0	0.0%	0	0 (0)	0.0% (0.0%)	0 (0)	1.0000

* Of the 152 subjects who participated in the US pivotal clinical study, 24 subjects were implanted with cone bearing pumps, including 2 subjects in whom pin bearing pumps were replaced by cone bearing pumps.

PMDA considers as follows:

(a) The purpose of changing the pin bearing pump to the cone bearing pump was to decrease the occurrence of thrombotic adverse events, but there was no statistically significant difference in the incidence of serious adverse events between the old model and Jarvik 2000 groups. However, considering that no pump replacement was required in the Jarvik 2000 group, PMDA would not deny the applicant's presumption that the incidence of thrombotic adverse events tended to be lower in Jarvik 2000 group although the sample size was limited and the comparison was based on point estimates. However, since subjects underwent implantation at different times between the 2 groups in the same clinical study, it cannot be ruled out that other factors, including effects from accumulated experiences of using the Jarvik 2000 VAD in clinical practice, may have influenced the results.

(b) Since the applicant's discussion has not compared all adverse events, PMDA reviewed whether Jarvik 2000 is associated with a higher risk of other adverse events than the

existing similar devices. No adverse events, excluding gastrointestinal haemorrhage, occurred at a higher incidence for the proposed product than for the existing similar devices (gastrointestinal haemorrhage is separately discussed and described in 8.B.[5]). Therefore, the results of Jarvik 2000 did not indicate that its safety is clearly inferior to the existing implantable ventricular assist devices indicated for severe heart failure for which no other treatment is available. However, the safety evaluation of Jarvik 2000 might not have been possible to the satisfactory extent due to a limited sample size.

In summary, although enough evaluation on the safety of Jarvik 2000 might not have been possible due to a limited sample size, PMDA concludes from the study results available to date that Jarvik 2000 is not associated with an unacceptable risk as an implantable ventricular assist device. However, it is important to collect post-marketing safety information to further secure the efficacy and safety of Jarvik 2000.

8.B.2.(2) Effects of difference in surgical approaches

Since Jarvik 2000 can be implanted through a left thoracotomy besides a median sternotomy, which is the common approach of other implantable ventricular assist devices, PMDA asked the applicant to explain effects of the difference in surgical approaches on the efficacy and safety of Jarvik 2000.

The applicant responded as follows:

The efficacy results in all subjects, including subjects implanted with the pin bearing pump, were compared between median sternotomy and left thoracotomy. As shown in Table 20, there was no substantial difference in the success rate at 180 days post-implantation between the 2 approaches. For the safety results, 16 serious adverse events occurred in the left thoracotomy group at an incidence of ≥2 times that in the median sternotomy group. The difference in the incidence (incidence in the left thoracotomy group minus incidence in the median sternotomy group) of device-related (including unspecified-cause) serious adverse events was 7.1% for haemolysis, 7.1% for thrombus in device, 11.4% for stroke, 7.1% for transient ischaemic attack, 7.1% for cardiovascular dysfunction, 7.1% for right heart failure, 14.3% for hepatic impairment, 7.1% for renal impairment, 11.4% for external device failure, 7.1% for reoperation due to haemorrhage, and 10.0% for procedure-related failure. However, these differences are possibly caused by the difference in the number of subjects in each group (more subjects undergoing a left thoracotomy than a median sternotomy). Moreover, the incidence of other serious adverse events was not markedly different between the 2 thoracotomy procedures although the difference in the number of subjects in each group and the incidence of 0% in 1 group influenced the difference in the incidences (Table 21).

PMDA concluded that neither surgical approach was associated with a clearly high incidence of adverse events or with an unacceptable risk although the effects of the difference in surgical approaches on the use results of Jarvik 2000 had not been fully assessed due to a limited sample size.

Table 20. Success rate at 180 days post-implantation by surgical approach for thoracotomy procedures and anastomotic site of the artificial blood vessel

Subject group Surgical approach/ anastomotic site	Pivotal clinical study/pin bearing pump		Pivotal clinical study/cone bearing pump	
	Number and percentage of subjects (relative frequency)	Cardiac transplantation, survival at 180 days (percentage)	Number and percentage of subjects (relative frequency) Upper, N = 24; lower, N = 17	Cardiac transplantation, survival at 180 days (percentage) Upper, N = 24; lower, N = 17
Median sternotomy, ascending aorta	41 (33.6%)	63.4% (26/41)	10 (41.7%)	100.0% (10/10)
			8 (47.1%)	100.0% (8/8)
Left thoracotomy, descending aorta	65 (53.3%)	66.2% (43/65)	14 (58.3%)	85.7% (12/14)
			9 (52.9%)	100.0% (9/9)
Others*	16 (13.1%)	62.5% (10/16)	0 (0.0%)	0.0% (0/0)
			0 (0.0%)	0.0% (0/0)
Total	122 (100%)	64.8% (79/122)	24 (100.0%)	91.7% (22/24)
			17 (100.0%)	100.0% (17/17)
Between-group difference	-	-	-	14.3% ($P = 0.62$)
			17 (100.0%)	0.0% ($P = 1.00$)

* In the early stage of the clinical study, various approaches (e.g., subcostal approach) were used.

Table 21. Adverse events by surgical approach for thoracotomy procedure (Jarvik 2000 group; the data for the re-consent group in parentheses)

Adverse event	Total number of subjects with event	Left thoracotomy, n = 14 (n = 9)		Median sternotomy, n = 10 (n = 8)	
		Number of subjects	Incidence	Number of subjects	Incidence
Excessive haemorrhage	2* (2)*	1* (1)*	7.1% (11.1%)	1 (1)	10.0% (12.5%)
Haemolysis	1* (1)*	1* (1)*	7.1% (11.1%)	0 (0)	0.0% (0.0%)
Thrombus in device	1* (1)*	1* (1)*	7.1% (11.1%)	0 (0)	0.0% (0.0%)
Thromboembolism (non-central nervous system)	0 (0)	0 (0)	0.0% (0.0%)	0 (0)	0.0% (0.0%)
Stroke	4 (1)	3 (1)	21.4% (11.1%)	1 (0)	10.0% (0.0%)
Transient ischaemic attack	2 (2)	2 (2)	14.3% (22.2%)	0 (0)	0.0% (0.0%)
Other neurological dysfunction	2 (1)	1 (0)	7.1% (0.0%)	0 (1)	0.0% (12.5%)
Infections	12* (8)*	8* (5)*	57.1% (55.6%)	4 (3)	40.0% (37.5%)
Cardiovascular dysfunction	1 (0)	1 (0)	7.1% (0.0%)	0 (0)	0.0% (0.0%)
Right heart failure	1 (0)	1 (0)	7.1% (0.0%)	0 (0)	0.0% (0.0%)
Hepatic impairment	3* (2)*	3* (2)*	21.4% (22.2%)	0 (0)	0.0% (0.0%)
Renal impairment	1* (1)*	1* (1)*	7.1% (11.1%)	0 (0)	0.0% (0.0%)
Gastrointestinal malfunction	1 (0)	1 (0)	7.1% (0.0%)	0 (0)	0.0% (0.0%)
Pulmonary function impairment	4 (2)	3 (1)	21.4% (11.1%)	1 (1)	10.0% (12.5%)
Reoperation	1 (1)	0 (0)	0.0% (0.0%)	1 (1)	10.0% (12.5%)
Requiring other surgical treatment	3 (3)	1 (1)	7.1% (11.1%)	2 (2)	20.0% (25.0%)
Failure of the implanted device	0 (0)	0 (0)	0.0% (0.0%)	0 (0)	0.0% (0.0%)
External device failure	4* (3)*	3* (2)*	21.4% (22.2%)	1 (1)	10.0% (12.5%)
Other adverse events	15* (12)*	8* (6)*	57.1% (66.7%)	7 (6)	70.0% (75.0%)
Reoperation due to haemorrhage	5 (3)	4 (2)	28.6% (22.2%)	1 (1)	10.0% (12.5%)
Unexpected adverse event	0 (0)	0 (0)	0.0% (0.0%)	0 (0)	0.0% (0.0%)
Coagulation disorder	0 (0)	0 (0)	0.0% (0.0%)	0 (0)	0.0% (0.0%)
Procedure-related failure	1 (1)	0 (0)	0.0% (0.0%)	1 (1)	10.0% (12.5%)
Neurocognitive disorder	2 (0)	2 (0)	14.3% (0.0%)	0 (0)	0.0% (0.0%)
Air embolism	0 (0)	0 (0)	0.0% (0.0%)	0 (0)	0.0% (0.0%)

* Including events that occurred during MCS with the pin bearing pump

8.B.2.(3) Use of protective artificial blood vessel

During the course of the review process, an additional artificial blood vessel was found to have covered the outflow artificial blood vessel of Jarvik 2000 in some subjects in the US pivotal and Japanese clinical studies to reinforce the one of Jarvik 2000.

PMDA asked the applicant to explain its background and situation of actual use.

The applicant responded as follows:

The use of an additional artificial blood vessel was not stated in the protocols of these studies. Nevertheless it was used to prevent kinking at the physician's discretion in clinical practice probably because the outflow artificial blood vessel of Jarvik 2000 is flexible and deformable. In the US pilot and pivotal clinical studies, kinks of the outflow artificial blood vessel occurred in a total of 6 subjects. Table 22 shows the use of additional artificial blood vessels in these subjects.

Table 22. Use of additional artificial blood vessels in subjects experiencing outflow artificial blood vessel kinking

Subject number	Use of additional artificial blood vessel	Body surface area (BSA)	Surgical Approach
US pilot clinical study			
1	No additional artificial blood vessel was used.	2.1 m^2	Median sternotomy
US pivotal clinical study			
2	No additional artificial blood vessel was used. The subject underwent reoperation to fix kinking of the outflow artificial blood vessel and received an artificial blood vessel with a ring.	2.1 m^2	Left thoracotomy
3	The same as above.	2.0 m^2	Left thoracotomy
4	The same as above.	1.6 m^2	Median sternotomy
5	No additional artificial blood vessel was used.	2.3 m^2	Median sternotomy
6	The subject was implanted with an additional artificial blood vessel together with a ring during implantation of the pump.	2.3 m^2	Median sternotomy

Because whether or not an additional protective artificial blood vessel was used in the US pilot and pivotal clinical studies cannot be confirmed from the case report forms etc., Jarvik Heart Inc., the manufacturer of the product and sponsor of these studies, interviewed the study sites about the use of protective artificial blood vessels. Although their use was unknown at many study sites, 10 of 21 participating medical institutions provided a definitive response and protective artificial blood vessels were used at 9 of them.

In the Japanese clinical study, artificial blood vessel for central circulation system (generic name), an artificial blood vessel approved in Japan, was used in all of 6 subjects when the investigational product was implanted to prevent the outflow artificial blood vessel from kinking.

PMDA considered that although the efficacy and safety of the combination use of the above artificial blood vessel and the outflow artificial blood vessel of Jarvik 2000 are unknown since such combination use was not expected, they were used concomitantly to reduce kinking, which is a fatal adverse event for ventricular assist devices, at the physician's discretion during actual clinical practice and it can be acceptable. Taking account that the results of the clinical studies of Jarvik 2000 were the results of concomitant use of the outflow artificial blood vessel and an additional artificial blood vessel, such use can be considered acceptable as a measure to reduce risk of kinking although it still occurred in 1 subject concomitantly implanted with a protective artificial blood vessel overseas. PMDA instructed the applicant to provide a protective artificial blood vessel as a concomitant device and recommend its use PMDA concluded that it is necessary to continue to collect the latest information on Jarvik 2000 used in Japan and overseas after the

market launch, and analyze the influence on the safety of Jarvik 2000 exerted by using or not using a protective artificial blood vessel, and consider further risk reduction measures.

The applicant accepted the PMDA's instructions and decided to add a protective artificial blood vessel to the components of Jarvik 2000.

8.B.2.(4) Risk of power disruption

Jarvik 2000 is powered by 1 battery. The Y-cable enables patients to change batteries without shutdown. However, the pump stops when the battery is dislocated inadvertently.

PMDA asked the applicant's view on the shutdown risk of Jarvik 2000 since power disruption can be caused by patients or caregivers and therefore risk reduction measures, including those for home therapy, are necessary.

The applicant responded as follows:

Since pump stoppage due to power disruption is associated with a serious risk directly related to patients' life support, the following "pump stop test" is required before discharging from hospital as a risk reduction measure for home therapy. The pump stop test described below is intended to confirm the patient tolerability to power disruption (3 minutes) during battery replacement. If the patient is considered eligible, training for home therapy is started.

Pump stop test

1) The physician stops the patient's pump for 3 minutes and confirms the absence of any hemodynamic problem.
2) Blood pressure and echocardiogram are monitored during 3-minute pump stoppage. Aortic valve opening/closing is checked on echocardiogram.

With the dedicated Y-cable (Figure 6: the arrows), the battery can be replaced while the pump is kept powered. One end of this Y cable (lower part of Y) is to be connected to the controller. The weak battery should be replaced by connecting a fully-charged battery to another branch of the Y-cable (Figure 6: arrow B) with the weak battery remaining connected to the original branch (Figure 6: arrow A). While both the weak battery and the fully-charged battery are connected to the Y-cable, the product is designed to be powered by the fully-charged battery. The controller detects power disruption and activates an alarm (continuous tone) if the weak battery or the cable is disconnected before the fully-charged battery is connected to the cable. This hazard avoidance mechanism of the product prompts the patient to resume power supply to the pump.

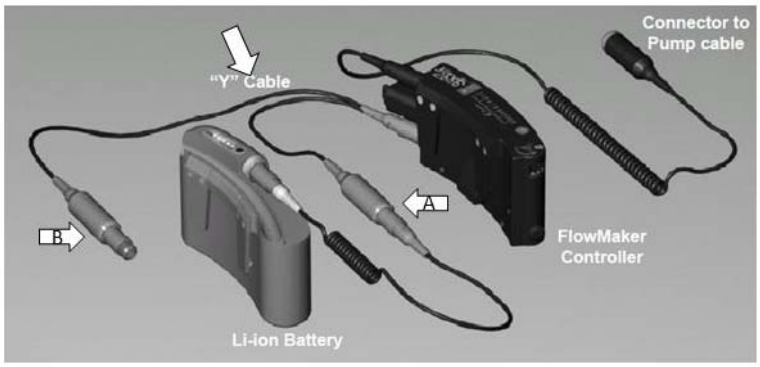

Figure 6. Components of Jarvik 2000

A total of 5 cases of power disruption occurred, including 3 cases in the US pilot clinical study

(N = 63) and 2 cases in the US pivotal clinical study (N = 152) (Table 23). In the Japanese clinical study, no events of power disruption occurred. The causes for power disruption were (a) disconnection between the internal and external cables (4 cases) and (b) no battery replacement (1 case).

(a) Disconnection between the internal and external cables was due to incorrect manipulation by patients or caregivers. The educational programs on device use and measures to be taken in case of disconnection were improved. This event can be human induced and caused by patients or caregivers and therefore has not been completely prevented yet. However, the incidence of the event decreased from 4.8% (3 events in 63 subjects) in the US pilot clinical study to 0.7% (1 event in 152 subjects) in the US pivotal clinical study.

(b) One case of no battery replacement occurred at 1 day post-implantation, which was likely due to inexperience in using the device. Healthcare professionals were again provided with a training on handling the device. This event did not occur after this case and the risk reduction measure seemed to be successful.

Table 23. Cases of power disruption in the US clinical studies (N = 215)

Event of power disruption	Number of events	Incidence
(a) Disconnection between the internal cable and the external cable	4	1.9%
(b) No battery replacement	1	0.5%
Total	5	2.3%

PMDA considered as follows:
The rotation of the pump in Jarvik 2000 immediately stops upon removal of the power source. Pump stoppage is a serious hazard directly related to patients' life support and therefore the highest possible level of safety measures is necessary to prevent its occurrence. First of all, thorough periodic training for patients and caregivers is essential. However, as power disruption was also reported with approved similar devices such as DuraHeart and HeartMate II, which are also powered by replaceable batteries, it is difficult to completely prevent the occurrence of inadvertent power disconnection even if patients and caregivers are thoroughly trained. The pump stop test only ensures the condition of the device before discharge from hospital. Considering possible changes in the patients' subsequent condition, the test does not assure successful battery replacement without patients' loss of consciousness when pumps actually stop.

On the other hand, unlike the approved similar devices, Jarvik 2000 is small and can be implanted via left thoracotomy. Jarvik 2000 may be a good treatment option for some patients.

Taking account of the above, introducing Jarvik 2000 in clinical practice is of clinical significance and the inherent risks of allowing the product of current specifications (the device being powered by 1 battery) to be marketed is not considered to outweigh the expected clinical usefulness of the product. However, since power disruption is a very serious event that may result in patient's death, PMDA decided to instruct the applicant to continue considering and take measures to reduce the risk of power disruption, including revising specifications as necessary, and designated this as Instruction 1.

8.B.2.(5) Gastrointestinal haemorrhage
Recent publications reported gastrointestinal haemorrhage as an adverse event specific to ventricular assist devices of axial flow type.[9,10] PMDA asked the applicant to explain this event.

The applicant responded as follows:
The occurrence of gastrointestinal haemorrhage in the Japanese clinical study, the US pilot and

pivotal clinical studies was investigated and the number of events in these studies were 0, 8, and 39 events, respectively (Table 24).

Table 24. Incidence of gastrointestinal haemorrhage in the US pilot and pivotal clinical studies

	Number of subjects (number of events)	Incidence	Causal relationship to the product (number of events)	
			Related	Unrelated
US pilot clinical study (N = 63)				
Non-serious	3 (4)	4.8%	0	4
Serious	4 (4)	6.3%	0	4
US pivotal clinical study (N = 152)				
Non-serious	5 (5)	3.3%	0	5
Serious	29 (34)	19.1%	1	33
Overall (N = 215)	41 (47)	19.1%	1	46

The incidence of serious gastrointestinal haemorrhage in the US pivotal clinical study was 19.1% (29 of 152 subjects). Except for 1 event in 1 subject, a causal relationship to the device was ruled out. However, axial flow-type ventricular assist devices are reportedly associated with a higher incidence of gastrointestinal haemorrhage than the non-axial flow type[11] likely because of decreased levels of von Willebrand factor and arteriovenous malformation (AVM) due to decreased pulse pressure caused by continuous flow. The von Willebrand factor is an important factor that triggers platelets to adhere and aggregate to the injured vascular endothelium. It is thought that this factor is destroyed by sheer stress arising from the rotor that rotates at a high speed inside the pump, resulting in suppressed platelet aggregation.[12] In the case of gastrointestinal haemorrhage, such as melena, appropriate tests and treatment are required considering potential haemorrhage from an AVM area. The risk of gastrointestinal haemorrhage as well as the necessity of appropriate tests and treatment should be mentioned in the instructions for use to raise cautions.

PMDA considered as follows:
Since a causal relationship to Jarvik 2000 was ruled out for all events of gastrointestinal haemorrhage observed after implantation of Jarvik 2000 in preclinical studies (bloody stool noted in 3 of 6 cows) and clinical studies and since no sufficient information is currently available regarding axial flow type-specific adverse event, there is no evidence sufficient to conclude that gastrointestinal haemorrhage is an adverse event specific to Jarvik 2000 or axial flow pumps.

Although the exact cause of gastrointestinal haemorrhage associated with the use of Jarvik 2000 still remains unknown, considering anticoagulant/antiplatelet therapy is given to patients during the use of Jarvik 2000, it is necessary to pay special attention to gastrointestinal haemorrhage. Since Jarvik 2000 can be used at home, it is also important for patients to visit medical institutions immediately when bloody stool, melena, and/or anemic symptoms develop. PMDA instructed the applicant to provide post-marketing information to healthcare providers in clinical settings so that physicians can endeavor to manage patient conditions with a special attention on gastrointestinal haemorrhage. Some literature suggests the involvement of gastrointestinal AVM in gastrointestinal haemorrhage.[13,14] However, even if gastrointestinal AVM is currently regarded as a high risk factor for gastrointestinal haemorrhage associated with Jarvik 2000, there is no established screening tool. For this reason, PMDA instructed the applicant to provide relevant information to healthcare providers in clinical settings to ensure that appropriate close examination and treatment are provided to patients when gastrointestinal haemorrhage, such as melena, occurs, considering that it can be caused by haemorrhage from a gastrointestinal AVM area.

8.B.3 Issues to be addressed when introducing the product to Japan

8.B.3.(1) Difference in waiting time to cardiac transplantation

Considering that there is a difference in the waiting time between in Japan and overseas, the applicant explained that Jarvik 2000 can continue to serve as an MCS during the waiting time to cardiac transplantation in Japan as follows:

The mean MCS duration before cardiac transplantation in 5 subjects implanted with the old model (pin bearing pump) in the Japanese extended study was 970 days. All of 5 subjects successfully underwent cardiac transplantation. In the US pilot clinical study (N = 63), the mean waiting time in 36 subjects who underwent cardiac transplantation was 126 days. In the US pivotal clinical study (N = 152), the mean waiting time in 82 subjects who underwent cardiac transplantation was 155 days. For Jarvik 2000 (cone bearing pump) only, the post-marketing long-term use in overseas was reported as follows: 73 subjects for ≥1 year; 41 subjects for ≥1 and <2 years; 25 subjects for ≥2 and <3 years; 7 subjects for ≥3 and <4 years (as of October 2013). On the other hand, the reported mean mechanical assist period in patients who underwent cardiac transplantation in Japan is 874 days[15] (Table 25).

The assist period in the Japanese extended clinical study is comparable to the mechanical assist period in patients who underwent cardiac transplantation in Japan, while the assist period before cardiac transplantation was shorter in both US clinical studies than in Japanese study. This is highly likely to have reflected a difference in the situation of cardiac transplantation between in Japan and overseas. Accordingly, based on the results of the Japanese extended clinical study in which the difference in the healthcare environment can be disregarded, it can be determined that Jarvik 2000 can continue to serve as an MCS during the waiting time in Japan.

Table 25. Comparison of mean assist period with Jarvik 2000 and mechanical assist period in Japan

		Mean
Jarvik 2000	Japanese extended clinical study (n = 5)	970 days
	US pilot clinical study (n = 36)	126 days
	US pivotal clinical study (n = 82)	155 days
Mechanical assist period in patients who underwent cardiac transplantation in Japan		874 days

Note) The numbers of subjects for the Japanese extended clinical study, the US pilot and pivotal clinical studies in the table represent the number of subjects who underwent cardiac transplantation.

Based on the result that 5 subjects successfully underwent cardiac transplantation after implantation of the old model (pin bearing pump) in Japan, where the reported waiting period is more than 2 years, and that 32 patients overseas received long-term MCS by Jarvik 2000 (cone bearing pump) for more than 2 years, PMDA concluded that Jarvik 2000 was expected to continue to serve as an MCS during a long waiting period for cardiac transplantation in Japan. However, it is important to collect post-marketing efficacy and safety information, including long-term prognosis, from more patients to further secure the efficacy and safety of Jarvik 2000, since Jarvik 2000 (cone bearing pump) has not yet been used in Japan and the long-term MCS by the product has not been evaluated in a sufficient number of patients.

8.B.3.(2) Use in small patients

Considering that many patients in Japan are smaller than patients in the US, PMDA asked the applicant to explain the usefulness of Jarvik 2000 in relatively small patients.

The applicant responded as follows:

In the Japanese clinical study (N = 6), the body surface area (BSA) was <1.5 m^2 in 2 subjects, who eventually underwent cardiac transplantation (outcome) (Table 26). These 2 subjects were on MCS for 983 and 1089 days and underwent cardiac transplantation. One of the 2 subjects experienced a serious adverse event of infection at the skin penetration site of the internal cable,

for which a causal relationship to Jarvik 2000 could not be ruled out. In the Japanese clinical study, 1 subject with a BSA of ≥1.5 m^2 also experienced infection at the skin penetration site (non-serious). In the Japanese extended clinical study, 2 subjects with a BSA of ≥1.5 m^2 experienced infection at the skin penetration site (serious) in which a causal relationship to Jarvik 2000 could not be ruled out but none in subjects with a BSA of <1.5 m^2. These results indicate low correlation between physical size and infection at the skin penetration site.

Table 26. Subjects with a body surface area of <1.5 m^2 in the Japanese clinical study

Outcome	Number of subjects
Cardiac transplantation	2

The results in 255 patients who received Jarvik 2000 in routine clinical practice in Europe between CE Mark certification in April 2005 and the end of [redacted] 20[redacted] were reviewed. Of 255 patients, 41 were implanted with the cone bearing pump and 3 of them had a BSA of <1.5 m^2. All of the 3 patients were still on MCS by Jarvik 2000 (survival) with assist periods of 58, 134, and 398 days (Table 27), and a mean assist period of 196.7 ± 178.5 days (Table 28). The mean assist period was 166.0 ± 117.9 days for all the 41 patients, 163.5 ± 115.0 days for 38 patients with a BSA ≥1.5m^2, and 178.8 ± 115.5 days for 33 surviving patients with a BSA of ≥1.5m^2, showing no BSA-dependent difference in the assist period. In addition, no effects of physical size on survival were suggested although the sample size was limited.

Table 27. List of subjects (implanted with the cone bearing pump) with a BSA of <1.5 m^2 in the European post-marketing surveillance

Subject ID	BSA (m^2)	Duration of MCS (days)	Outcome
[redacted]	1.41	134	On MCS (survival)
[redacted]	1.39	398	On MCS (survival)
[redacted]	1.48	58	On MCS (survival)

Table 28. Assist period by Jarvik 2000 (subjects implanted with the cone bearing pump) in the European post-marketing surveillance

	Number of subjects	Duration of MCS (days)	Survival
Total	41	166.0 ± 117.9	87.8% (36/41)
BSA <1.5 m^2	3	196.7 ± 178.5	100% (3/3)
BSA ≥1.5 m^2	38	163.5 ± 115.0	86.8% (35/38)
BSA ≥1.5 m^2, subjects who survived	33	178.8 ± 115.5	-

In summary, physical size (BSA <1.5 m^2) is unlikely to affect the efficacy and safety of Jarvik 2000. Jarvik 2000 can be indicated for small patients (BSA <1.5 m^2) as well.

PMDA concluded that the actual use results in patients with a BSA of <1.5 m^2 does not rule out the use of Jarvik 2000 in relatively small patients although the sample size was limited. PMDA considered that no specific numerical criteria, including BSA, should be provided since the patient's eligibility for implantation of Jarvik 2000 should be determined based not only on BSA but also on the space around the implantation site, heart size, etc., and instructed the applicant to provide a caution that comprehensive judgment of an experienced physician is required in selecting patients. The applicant accepted the PMDA's instructions.

8.B.4 Post-marketing safety measures

PMDA asked the applicant to explain necessary measures to ensure proper use by patients and caregivers after Jarvik 2000 is launched in the market.

The applicant responded as follows:

As necessary measures to ensure proper use by patients and caregivers after Jarvik 2000 is launched in the market, a training program for Jarvik 2000 was planned to be provided. This training program is intended to ensure safe home care and therapy of patients. Healthcare professionals at medical institutions are responsible for providing patients and caregivers with training.

Figure 7 illustrates the procedures of the training program. This training program was also used in the Japanese clinical study.

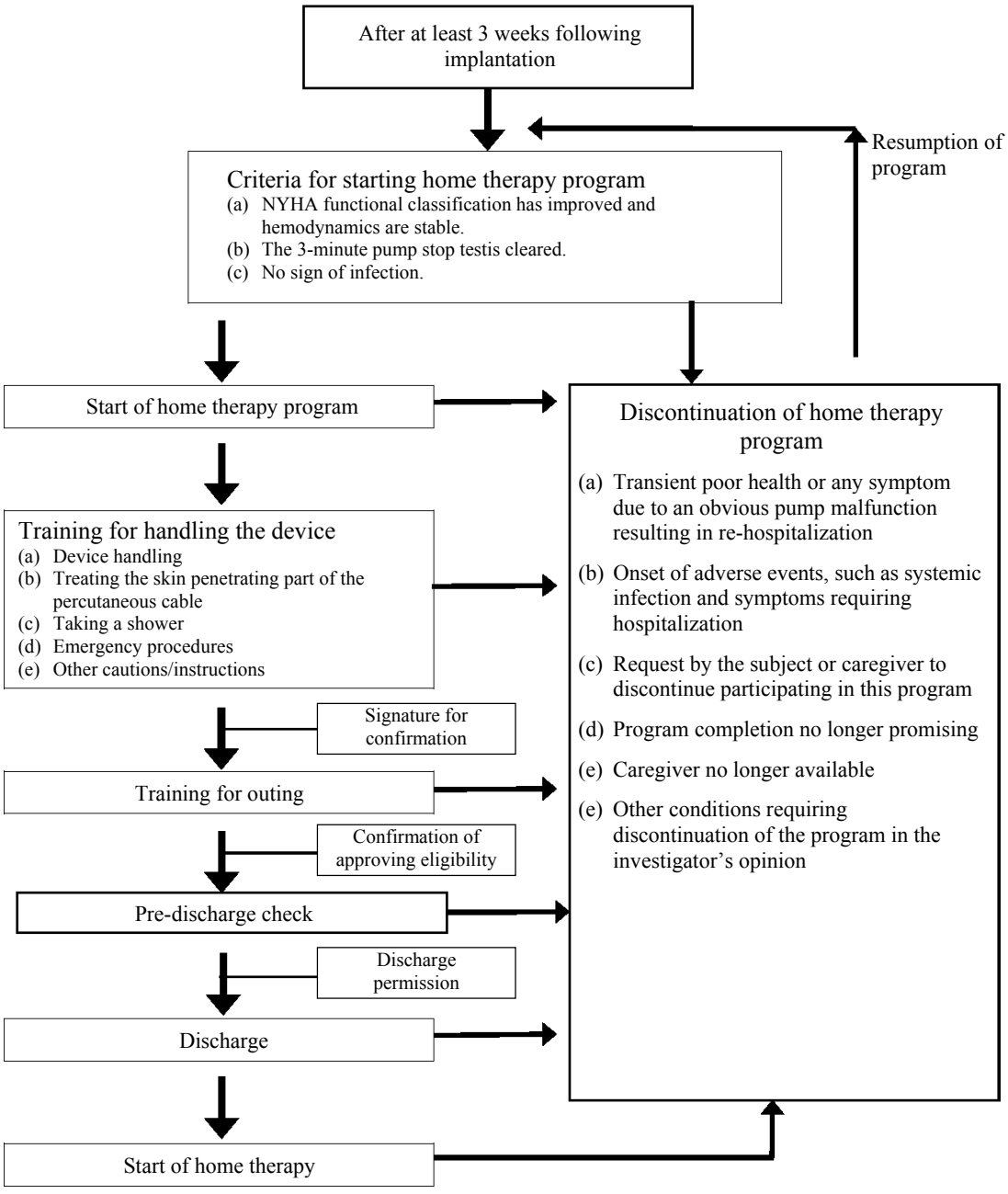

Figure 7. Home therapy training flow

PMDA considers as follows:
Jarvik 2000 is directly related to patients' life support and intended to be used outside medical institutions. Healthcare professionals, patients, and their caregivers must 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. However, since accidents, including power loss due to inadvertent battery disconnection or drained battery, occurred in the US and Japanese clinical studies, it is difficult to completely eliminate human errors even with thorough training. It is necessary to ensure that patients and caregivers are provided with a thorough post-marketing training program similar to that for the clinical study, to provide healthcare professionals, patients, and their caregivers with sufficient information regarding problems reported in the US and Japanese clinical studies and after the market launch, to consider further risk reduction measures, and to improve training, support system, etc., as necessary.

In conclusion, the results of the US pivotal clinical study, the Japanese clinical study, etc., demonstrate that the efficacy and safety of Jarvik 2000 in patients eligible for cardiac transplantation in Japan are not inferior to those of the approved implantable ventricular assist devices and are acceptable. The essential points suggested for the safety measures of Jarvik 2000 include the use of the product only by qualified physicians/medical institutions and establishment and maintenance of an appropriate training and support system. Since physicians and medical institutions have to fully understand Jarvik 2000 to ensure its efficacy and safety, the following condition must be fulfilled for approval: necessary measures must be taken to ensure that Jarvik 2000 is used by physicians who fully understand the efficacy and safety of the product and have sufficient knowledge and experience in implantation techniques, etc., at qualified medical institutions.

In addition, it is important to collect post-marketing efficacy and safety information, including long-term prognosis, from more patients to further secure the efficacy and safety of Jarvik 2000, since the Japanese clinical study was conducted in a limited number of subjects, did not use the cone bearing pump, included limited analysis of the long-term safety of Jarvik 2000, did not provide sufficient information about adverse events specific to axial flow pumps, and did not fully evaluate the efficacy and safety of using the protective artificial blood vessel. Accordingly, PMDA determined that this statement should be included in the conditions for approval. Finally, since Jarvik 2000 is directly related to the patients' life support and is highly predictable to be used outside medical institutions, PMDA concluded that the following conditions for approval should be imposed: the applicant is required to ensure the safety of the product 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

[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 (H-1-3). As a result, the results recorded in the case report forms were not appropriately reflected in the clinical study report and the list of subjects. PMDA concluded that although the above issue needed to be improved, there should be no problem with conducting a regulatory review based on the submitted product application documents, including the modified data that were re-summarized and submitted.

[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-1-1, H-1-3). As a result, protocol deviations (no conduct of measurement using NIH Stroke Scale, Neurocognitive studies, and Quality of Life Questionnaire) were found at some medical institutions. Although the above issue needed to be improved, appropriate measures were taken for the concerned subjects and overall the study was conducted according to the GCP. PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

[Others]
In the course of regulatory review of Jarvik 2000, the description in the written explanation used to obtain informed consent from subjects in the US pivotal clinical study was found to be insufficient. The applicant rearranged the data of the marketing application form to include the results of analysis only in subjects who gave re-consent based on the additional written information. Consequently, it took more than 1 year for the applicant to submit the revised data and for PMDA to start the document-based compliance assessment and GCP on-site inspection. In addition, after starting the document-based compliance assessment, it was found out that the results recorded in the case report forms were not appropriately reflected in the submitted data. Thus, almost another 6 months was spent on repeated modifications and re-summarization.

PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents that were rearranged, but determined that a system needs to be established to prevent recurrence of similar mishandlings and instructed the applicant to take preventive measures.

The applicant responded that they would establish such systems in the future and PMDA accepted it.

V. Overall Evaluation

Jarvik 2000 Implantable Ventricular Assist Device is an implantable ventricular assist device intended for use to improve blood circulation in patients with end-stage severe heart failure who require cardiac transplantation.

The major issues discussed in the regulatory review of Jarvik 2000 were as follows: (1) the efficacy of the product; (2) the safety of the product; (3) post-marketing safety measures; and (4) the long-term efficacy and safety of the product.

(1) In the US pivotal clinical study, the success rate of MCS at 180 days post-implantation or until cardiac transplantation was 100% (17 of 17 subjects) in those who were implanted with Jarvik 2000 and provided re-consent to GCP inspection by the Japanese regulatory authority. It should be noted that only subjects who provided re-consent were included in this analysis. The success rate of MCS at 180 days post-implantation or until cardiac transplantation was 91.7% (22 of 24 subjects) in those implanted with Jarvik 2000. In the Japanese clinical study, the success rate of MCS at 180 days post-implantation was 83.3% (5 of 6 subjects). Although it is difficult to simply compare the efficacy of the device with that of approved products because of differences in the subject's baseline characteristics, the times of the studies, countries where the studies were conducted, etc., the efficacy of Jarvik 2000 as an implantable ventricular assist device is not substantially inferior to that of the approved products.

(2) The causes of deaths in subjects receiving Jarvik 2000 were not substantially different from those reported for subjects receiving the other implantable ventricular assist devices, although the numbers of dead subjects were limited. The trend of adverse events observed in subjects receiving Jarvik 2000 was not substantially different from that in subjects receiving the other implantable ventricular assist devices. Since Jarvik 2000 is characterized by the fact that it needs no space for placing the pump in the abdomen, is light and small, and can be implanted through a left thoracotomy, PMDA considered it clinically significant to introduce Jarvik 2000 in the clinical practice.

(3) Considering the use results of other implantable ventricular assist devices approved in Japan as well, implantable ventricular assist devices may inevitably cause adverse events due to not only the seriousness of the target disease but also the nature of the products. To ensure safe and effective use of Jarvik 2000, it is important to appropriately handle malfunctions or adverse events of the product occurring after the market launch to minimize the health hazard to patients. For this purpose, it is critical to ensure that immediate measures are taken for malfunctions and that Jarvik 2000 is used by physicians who fully understand the product at qualified medical institutions. Furthermore, patients implanted with Jarvik 2000 and their caregivers have to fully understand the product and handle problems encountered appropriately during home therapy. Accordingly, PMDA determined that the following condition should be included as Condition for Approval 1: the applicant is required to take necessary measures to ensure that Jarvik 2000 is used by physicians who fully understand the product at qualified medical institutions.

Jarvik 2000 is possibly associated with the risk of patient's death when the pump stops due to battery dislocation. PMDA decided to instruct the applicant to periodically hold training sessions to ensure that patients fully understand that the disconnection of the battery may result in death and to take measures for reducing the risk of power disruption, including revising specifications, when necessary (Instruction 1). The applicant accepted Instruction 1.

Since Jarvik 2000 is expected to be used outside medical institutions, PMDA concluded that providing sufficient training etc., to healthcare professionals, patients, and their caregivers through home-therapy programs and establishing a sufficient support system should be included in the conditions for approval (Condition for Approval 3).

(4) Considering the current situation of cardiac transplantation in Japan, Jarvik 2000 is expected to be used for MCS for a prolonged period of time. Despite the fact that the product was used for long-term MCS over 2 years overseas, the long-term efficacy and safety of Jarvik 2000 have not been fully evaluated and no data are available regarding the use-results of the product in Japan. Thus, PMDA decided to add Condition for Approval 2 shown below to carefully observe long-term prognosis.

Based on the above discussion, PMDA considered that Jarvik 2000 is not inferior to DuraHeart, EVAHEART, or HeartMate II approved in Japan in terms of usefulness as an implantable ventricular assist device for a bridge to cardiac transplantation and that introducing the product in clinical practice, as with these approved devices, is beneficial for patients. PMDA concluded that the product may be approved after modifying the intended use in the "Intended Use, Indications" section in the submitted application form as shown below to be consistent with that of DuraHeart, EVAHEART, and HeartMate II, with following conditions for approval.

[Intended use]
Jarvik 2000 Implantable Ventricular Assist Device is used to improve blood circulation until cardiac transplantation is performed in patients who have severe heart failure eligible for cardiac transplantation, and show continuous decompensation in spite of drug therapy or mechanical circuratory support, 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. Establish appropriate qualification criteria for medical institutions and physicians in cooperation with related academic societies, and take necessary measures to limit the use of the product to physicians who have sufficient knowledge and experience in implantation of ventricular assist devices at qualified medical institutions.

2. Perform a use-results survey in all patients receiving the product in cooperation with related academic societies, and report the results of long-term outcome analysis to the Pharmaceuticals and Medical Devices Agency, as well as take appropriate measures as necessary.

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

Jarvik 2000 Implantable Ventricular Assist Device is a new performance medical device 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. The product is not classified as a biological product or a specified biological product. The product should be designated as a specially designated medical device and be tracked.

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

[Instructions]
1. Continuously consider the measures for reducing power disruption risk and take further measures as necessary.

References

[1] *Vital Statistics of Japan 2012*. Ministry of Health, Labour and Welfare
[2] *Statistical Abstract of the United States*. US Department of Commerce
[3] Frazier OH, Rose EA, OzMC, Dembitsky W, McCarthy P, Radovancevic B, et al. Multicenter clinical evaluation of the HeartMate vented electric left ventricular assist System in patients awaiting heart transplantation. *J Thorac Cardiovasc Surg.* 2001 Dec;122(6):1186-95.
[4] El-Banatosy A, Korfer R, Arusoglu L, Kizner L, Morshuis M, Milting H, et al. Device and patient management in a bridge-to-transplant setting. *Ann Thorac Surg.* 2001 Mar;71(3 Suppl):S98-102.
[5] El-Banayosy A, Arusoglu L, Kizner L, Tenderich G, Minami K, Inoue K, et al. Novacor left ventricular assist system versus Heartmate vented electric left ventricular assist system as a long-term mechanical circulatory support device in bridging patients: a prospective study. *J Thorac Cardiovasc Surg.* 2000 Mar;119(3):581-7.
[6] DiBella I, Pagani F, Banfi C, Ardemagni E, Capo A, Klersy C, et al. Results with the Novacor assist system and evaluation of long-term assistance. *Eur J Cardiothorac Surg.* 2000 Jul;18(1):112-6.
[7] Minami K, El-Banayosy A, Sezai A, Arusoglu L, Sarnowsky P, Fey O, et al. Morbidity and outcome after mechanical ventricular support using Thoratec, Novacor, and HeartMate for bridging to heart transplantation. *Artif Organs.* 2000 Jun;24(6):421-6.
[8] Farrar DJ, Hill JD, Pennington DG, McBride LR, Holman WL, Kormos RL, et al. Preoperative and postoperative comparison of patients with univentricular and biventricular support with the Thoratec ventricular assist device as a bridge to cardiac transplantation. *J Thorac Cardiovasc Surg.* 1997 Jan;113(1):202-9.
[9] Meyer AL et al, Acquired von Willebrand Syndrome in Patients With an Axial Flow Left Ventricular Assist Device. *Circulation: Heart Failure*. 2010;3:675-81.
[10] Uriel N et al, Acquired von Willebrand syndrome after continuous-flow mechanical device support contributes to a high prevalence of bleeding during long-term support and at the time of transplantation. *J Am Coll Cardiol*. 2010; 56(15):1207-13.
[11] Toda K. Current situation of implantable ventricular assist device HeartMate II. *Shinzo*. 2011;43:865-870.
[12] Crow S et al. Acquired von Willebrand syndrome in continuous-flow ventricular assist device recipients. *Ann Thorac Surg*. 2010;90:1263-1269.
[13] Letsou GV, Shah N, Gregoric ID, Myers TJ, Delgado R, Frazier OH. Gastrointestinal bleeding from arteriovenous malformations in patients supported by the Jarvik 2000 axial-flow left ventricular assist device. *J Heart Lung Transplant*. 2005;24:105-9.
[14] Demirozu ZT et al. Arteriovenous malformation and gastrointestinal bleeding in patients with the HeartMate II left ventricular assist device. *J Heart Lung Transplant.* 2011;30(8):849-53.
[15] *Organ Transplantation Fact Book 2012*. The Japan Society for Transplantation