Report on the Deliberation Results

June 29, 2018

Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

Classification	Instrument & Apparatus 29 Electrosurgical Unit
Term Name	Radiofrequency Ablation System
Brand Name	RFA System
Applicant	Boston Scientific Japan K.K.
Date of Application	December 25, 2017 (Application for Partial Change Approval)

Results of Deliberation

In its meeting held on June 29, 2018, the Committee on Medical Devices and *In-vitro* Diagnostics made the following decision, and concluded that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product may be approved under the following conditions, and the product should not be designated as a medical device subject to use-results evaluation. The product is not classified as a biological product or a specified biological product.

Conditions of Approval of Partial Change Application

The applicant is required to take necessary actions, including providing training sessions and disseminating guidelines on proper use prepared in cooperation with relevant academic societies, to ensure that the product will be used by physicians with thorough knowledge and experience in radiofrequency ablation of acardiac twinning who have acquired skills required for using the RFA System and adequate knowledge of procedural complications, in compliance with the intended use and directions for use, at medical facilities capable of providing adequate medical care.

Review Report

June 6, 2018
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following medical device submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency.

Classification	Instrument & Apparatus 29 Electrosurgical Unit
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Reviewing Office	Office of Medical Devices II

Review Results

Classification	Instrument & Apparatus 29 Electrosurgical Unit
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Results of Review

The RFA System is a radiofrequency ablation system used to coagulate and ablate malignant liver tumor or an acardiac twin (for acardiac twinning, the device is used only to stop blood flow to the acardiac twin). The device consists of electrodes, which are to be inserted into tissue for coagulation and ablation, and a generator, which delivers power to the electrodes. In acardiac twinning, a normally developing fetus (hereinafter referred to as the "pump twin"*) may supply blood to the acardiac twin (mass of tissue that has no potential for *exo utero* survival due to absence of organ structures) through abnormal vascular anastomosis in the placenta. If this condition progresses, an excessive load is imposed on the heart of the pump twin, leading to cardiac failure and eventually to death. The RFA System was already approved on March 2, 2005 for the indication of "malignant liver tumor" (approval number, 21700BZY00127000). The objective of the present application for partial change approval is to add an indication of "an acardiac twin (only for the purpose of blocking the blood flow to the acardiac twin)."

The applicant submitted non-clinical data for the RFA System (the results of testing of electrical safety and electromagnetic compatibility); the data revealed no particular problems. The data on physicochemical properties, biological safety, mechanical safety, and stability and durability were not submitted because the data submitted for the initial approval can be used for evaluation of the indication requested in the present application.

As data relating to clinical studies of the RFA System, the applicant submitted a clinical evaluation report, which was prepared based on 13 reports summarizing the outcomes of untreated pump twins (expectant management), and 12 reports (710 patients in total) summarizing treatment of acardiac twinning by radiofrequency ablation (RFA) using RFA devices including the RFA System. The following data demonstrated the efficacy of the RFA System in saving the lives of pump twins: (1) the pump twin survival rate was approximately ≥80% in RFA-treated pump twins (including those treated with the RFA System), in contrast to 42.9% in pump twins under expectant management; (2) 87.5% (35 of 40) of pump twins treated with the RFA System in Japan survived. In terms of safety, thermal burns at the site of grounding pads, and infections have been reported as maternal adverse events, while

* The normal fetus is referred to as the "pump twin" because its heart is used to pump blood to the acardiac twin.

premature rupture of membranes and premature delivery as adverse events in pump twins. Thermal burns at the site of grounding pads were considered to be preventable by paying attention to the location and number of grounding pads and to their unintentional removal from the skin, whereas risks for infections can be reduced by disinfection and administration of antibiotics. The use of the RFA System involves a certain degree of risk for premature rupture of membranes and premature delivery. Nevertheless, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the RFA System has acceptable clinical safety, because the outcome of pump twins is reported to be extremely poor if they are managed expectantly despite being eligible for RFA treatment.

Based on comments from the Expert Discussion, PMDA reviewed the data submitted in a comprehensive manner. As a result, PMDA has concluded that, given the rarity of acardiac twinning, treatment with the RFA System, as a life-saving device for pump twins, has benefits that outweigh the risks, provided that the device is used in compliance with the guidelines on proper use to be prepared by relevant academic societies.

On the basis of its regulatory review, PMDA has concluded that the RFA System may be granted marketing approval for the following intended use under the conditions of approval shown below, and that this result should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

Intended Use

Radiofrequency coagulation and ablation of the following tissues:

1. Malignant liver tumor
2. Acardiac twinning (only for the purpose of blocking the blood flow to the acardiac twin)

Conditions of Approval

The applicant is required to take necessary actions, including providing training sessions and disseminating guidelines on proper use prepared in cooperation with relevant academic societies, to ensure that the product will be used by physicians with thorough knowledge and experience in radiofrequency ablation of acardiac twinning who have acquired skills required for using the RFA System and adequate knowledge of procedural complications, in compliance with the intended use and directions for use, at medical facilities capable of providing adequate medical care.

Review Report

June 6, 2018

Product for Review	
Classification	Instrument & Apparatus 29 Electrosurgical Unit
Term Name	Radiofrequency Ablation System
Brand Name	RFA System
Applicant	Boston Scientific Japan K.K.
Date of Application	December 25, 2017
Proposed Intended Use	Radiofrequency energy coagulation of the following tissues: 1. Malignant liver tumor 2. Acardiac twins

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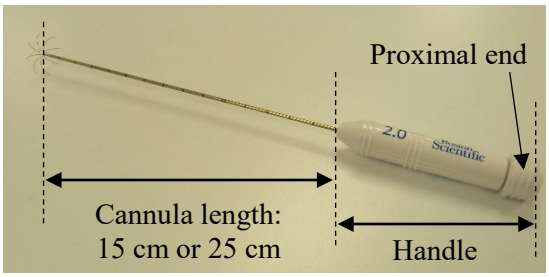
List of Abbreviations

MFICU	Maternal-fetal intensive care unit
RFA	Radiofrequency ablation
SMFM Clinical Guideline	Society for Maternal-Fetal Medicine Clinical Guideline
TRAP sequence	Twin reversed arterial perfusion sequence

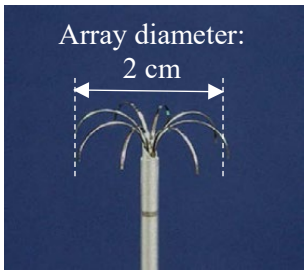
I. Product Overview

The RFA System is a radiofrequency ablation system used to coagulate and ablate malignant liver tumor or an acardiac twin (for acardiac twinning, the device is used only to stop blood flow to the acardiac twin). The device consists of electrodes, which are to be inserted into tissue for coagulation and ablation, and a generator, which delivers power to the electrodes (Figure 1). Acardiac twinning is characterized by the coexistence of a normally developing fetus (hereinafter referred to as the "pump twin"*) and an acardiac twin (mass of tissue that has no potential for *exo utero* survival due to absence of organ structures) *in utero*. Acardiac twinning may present with twin reversed arterial perfusion (TRAP) sequence, a condition in which the pump twin supplies blood to the acardiac twin through abnormal vascular anastomosis in the placenta. If this condition progresses, an excessive load is imposed on the heart of the pump twin, leading to cardiac failure. It is therefore necessary to stop blood flow to the acardiac twin to save the life of the pump twin. In the RFA procedure, the electrode cannula is inserted through the maternal abdominal wall under ultrasound guidance, advanced into the uterus, and inserted further into the area near the umbilical cord insertion site of the acardiac twin. Coagulation and ablation is performed at the distal tip of the cannula with radiofrequency energy to block blood flow from the pump twin to the acardiac twin (Figure 2). The electrodes are available in 2 cannula lengths (15 and 25 cm) so as to accommodate the varying distance between the maternal abdominal wall and the acardiac twin. The distal tip of the electrode cannula has an umbrella-shaped array design to allow outward expansion of tines (Figure 1 "Electrode [distal tip of the cannula]). After insertion, when the user pushes the proximal end of the electrode handle in the direction of the mother's body, the distal tip array is deployed.

* The normal fetus is referred to as the "pump twin" because its heart is used to pump blood to the acardiac twin.



Electrode (overall view)



Electrode (distal tip of the cannula)

- Dimension

Height	Width	Depth
11 cm	36 cm	42 cm

- Electrical rating

Rated voltage	Frequency	Power input
AC100-120 V	50/60 Hz	4.8 A

- Radiofrequency specifications

Output frequency	Output power	Time display range
461 ± 5 kHz	Max: 200 W	0-20 minutes

Generator

Figure 1. Appearance of the RFA System

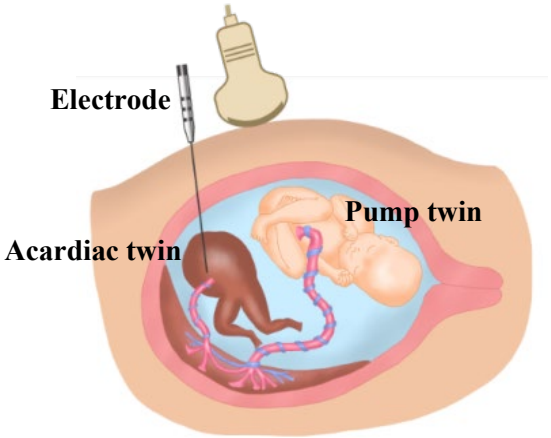


Figure 2. Radiofrequency ablation of the acardiac twin

The RFA System received approval on March 2, 2005 for the indication of "malignant liver tumor" (approval number, 21700BZY00127000). The applicant subsequently submitted the present partial change application to add a new indication, "acardiac twin," with no changes in specifications or components of the RFA System.

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

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

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

1. History of Development, Use in Foreign Countries, and Other Information

1.A. Summary of the data submitted

1.A.(1) History of development

Acardiac twinning is a condition unique to monochorionic twin pregnancies (twins sharing a single placenta), and is characterized by the coexistence of a normally developing pump twin and an acardiac twin *in utero*. An acardiac twin is a mass of tissue with no human organ structures, and has no potential for *exo utero* survival. Some acardiac twins, however, continue to grow when blood is supplied by the pump twin through arterio-arterial anastomosis or veno-venous anastomosis in the placenta; this condition is called TRAP sequence. The pump twin has to pump blood to not only its own systemic circulation but also the acardiac twin. This condition increases cardiac load in the pump twin and, in severe cases, may lead to fetal or neonatal death due to high-output cardiac failure.

Acardiac twinning is reported to occur in 1 in 35,000 births.[i] In Japan, where there are approximately 1 million births every year, approximately 30 cases of acardiac twinning is estimated to occur each year. Of these, approximately 15 to 20 cases per year are eligible for the treatment with the RFA System.

Since the 1990s, physical interventions to interrupt perfusion of the acardiac twin, the cause of excessive cardiac load on the pump twin, have been performed in order to save the life of the pump twin. These treatment techniques include (a) umbilical cord occlusion, in which the umbilical cord is occluded fetoscopically using bipolar forceps, and (b) coagulation of the acardiac twin by radiofrequency or laser to interrupt perfusion of the acardiac twin. Among the coagulation techniques for acardiac twinning, radiofrequency ablation (RFA) has become the mainstream technique today both in and outside Japan. RFA of the acardiac twin is mentioned in textbooks, guidelines, and other publications on obstetrics and gynecology, and fetology published in and outside Japan. Radiofrequency ablation of the acardiac twin is recommended in the following guidelines: "Guidelines for Obstetrical Practice in Japan. 2017 edition (Japan Society of Obstetrics and Gynecology/Japan Association of Obstetricians and Gynecologists),"[ii] and "Society for Maternal-Fetal Medicine Clinical Guideline. #7: nonimmune hydrops fetalis: 2015 (SMFM Clinical Guideline)."[iii] In Japan, however, no RFA devices have been approved for coagulation of the acardiac twin, and thus RFA devices are used off-label.

The RFA System was developed for thermal coagulation of soft tissue. In Japan, the RFA System received approval on March 2, 2005 for the indication of "malignant liver tumor" (approval number, 21700BZY00127000). In response to the growing need for expanding the indication of RFA devices to include acardiac twinning in Japan, the applicant submitted a partial change application, to ensure that

acardiac twinning can be treated by the RFA System with the tissue coagulation techniques currently used to treat malignant liver tumors.

A petition for early introduction of RFA for acardiac twinning has been submitted by the Japanese Society of Fetal Therapy, Japan Society of Obstetrics and Gynecology, and Japan Society of Perinatal and Neonatal Medicine in relation to the present application.

1.A.(2) Use in and outside Japan

In Japan, the RFA System was approved on March 2, 2005 for the intended use, "coagulation of malignant liver tumor with radiofrequency energy." In Europe and the US, the RFA System has been approved for the intended use shown in Table 1.

Table 1. Intended use and approval dates in Europe and the US

Country/region	Intended use	Date of approval
US	Thermal coagulation of soft tissue	April 2000 (K000241)
Europe		September 2000

In Japan, [redacted] electrodes and [redacted] generators were on sale between March 2005 and June 2017. In the US and Europe, [redacted] electrodes and [redacted] generators were on sale between December 2005 and June 2017.

1.A.(3) Malfunctions in and outside Japan

Tables 2 through 4 show the incidence of malfunctions in and outside Japan.

In Japan, there were no reports of malfunctions caused by generators.

Table 2. Malfunctions in Japan (electrodes) (March 2005 to June 2017)

Type of malfunction/adverse event	Number of incidents	Incidence[*1] (%)
Death[*2]	[redacted]	0.011
Damage to insulation coating	[redacted]	0.126
Failure to retract the deployed array	[redacted]	0.045
Unknown	[redacted]	0.018
Defect or possible defect of insulator coating	[redacted]	0.004
Suspected damage to insulation coating	[redacted]	0.002
Molding defect of insulation coating/removal of insulation coating	[redacted]	0.002
Detachment of deployed array	[redacted]	0.002
Deployment failure	[redacted]	0.002

[*1], Incidence (%) = (number of incidents / [redacted]) × 100
[*2], Death in [redacted] was unrelated to the RFA System.
Death in [redacted] was due to local recurrence with an unknown relationship to the RFA System.
Death in [redacted] was due to an unknown cause with an unknown relationship to the RFA System.

Table 3. Malfunctions in foreign countries (electrodes)
(December 2005 to June 2017)

Type of malfunction/adverse event	Number of incidents	Incidence[*1] (%)
Death[*2]	[redacted]	0.0035
Thermal burn at the site of the grounding pad[*3]	[redacted]	0.0248
Thermal burn around the needle/insertion site[*4]	[redacted]	0.0205
Complication[*5]	[redacted]	0.0120
Discomfort/pain[*6]	[redacted]	0.0071
Thermal burn[*7]	[redacted]	0.0057
Inflammation[*8]	[redacted]	0.0042
Pleural effusion[*9]	[redacted]	0.0042
Pyrexia[*10]	[redacted]	0.0035
Haemorrhage/exsanguination with sequelae[*11]	[redacted]	0.0028
Surgery[*12]	[redacted]	0.0028
Haematoma[*13]	[redacted]	0.0021
Injury[*14]	[redacted]	0.0021
Perforation (nonvascular)[*15]	[redacted]	0.0021
Arrhythmia[*16]	[redacted]	0.0014
Dyspnoea[*17]	[redacted]	0.0007
Fistula[*18]	[redacted]	0.0007
Medical intervention[*19]	[redacted]	0.0007
Pneumothorax[*20]	[redacted]	0.0007
Thrombosis (untreated blood vessel)[*21]	[redacted]	0.0007
Insufficient roll-off	[redacted]	0.0106
Damage to insulation coating/insulation coating peeled off	[redacted]	0.0071
Wrong use/user error	[redacted]	0.0042
Defect/malfunction	[redacted]	0.0035
Electrode deformation	[redacted]	0.0028
Difficulty in retracting the needle electrode	[redacted]	0.0028
Postponement of surgery	[redacted]	0.0014
Foreign body remnant	[redacted]	0.0014
Dislodged component	[redacted]	0.0014
Difficulty in deploying the expandable distal tip of the electrode	[redacted]	0.0007
Error message	[redacted]	0.0007
Foreign body	[redacted]	0.0007
Unknown	[redacted]	0.0007

[*1], Incidence (%) = (number of incidents / [redacted]) × 100
[*2], Death in [redacted] was unrelated to the RFA System.
Death in [redacted] was due to bowel perforation with an unknown relationship to the RFA System.
Death in [redacted] was due to postoperative bleeding with an unknown relationship to the RFA System.
An alert has already been issued for possible perforation and tissue injury during insertion.
[*3-21], Unrelated to the RFA System.

Table 4. Malfunctions in foreign countries (generator)
(December 2005 to June 2017)

Type of malfunction/adverse event	Number of incidents	Incidence[*1] (%)
Thermal burn at the site of the grounding pad[*2]	[redacted]	5.97
Thermal burn[*3]	[redacted]	1.02
Thermal burn around the needle/insertion site[*4]	[redacted]	0.68
Complication[*5]	[redacted]	0.17
Fistula[*6]	[redacted]	0.17
Haemorrhage[*7]	[redacted]	0.17
Thrombosis (untreated blood vessel)[*8]	[redacted]	0.17
Defect/malfunction	[redacted]	0.34
Error message	[redacted]	0.17
Insufficient roll-off	[redacted]	0.17
Wrong use/user error	[redacted]	0.17

[*1], Incidence (%) = (number of incidents / [redacted]) × 100
[*2-8], Unrelated to the RFA System.

2. Design and Development

2.(1) Performance and safety specifications

2.(1).A Summary of the data submitted

The present partial change application has proposed performance and safety specifications presented below. These specifications are the same as those approved at the initial approval because since then no changes have been made to the specifications or components of the RFA System.

The proposed specifications for the performance of the electrode include [redacted], damage and appearance, and [redacted]. The proposed specifications for the performance of the generator include output frequency, output power, resistance measurement range, and time display range. The proposed specifications for the safety of the electrode include electrical safety (IEC60601-1:2007, IEC60601-2-2:2009), electromagnetic compatibility (IEC60601-1-2:2010), biological safety, sterility assurance, and ethylene oxide sterilization residuals. The proposed specifications for the safety of the generator include electrical safety (IEC60601-1:2007, IEC60601-2-2:2009) and electromagnetic compatibility (IEC60601-1-2:2010).

2.(1).B Outline of the review conducted by PMDA

Among the proposed performance and safety specifications, the performance specifications are the same as those approved at the initial approval. The following passage describes PMDA's view on using the same performance specifications as those approved at the initial approval:

The following is the performance required for the RFA System to perform RFA of the acardiac twin: the electrode cannula must be capable of being inserted via the maternal abdominal wall into the acardiac twin, and the device must be capable of coagulating and ablating target tissue as intended. The area

through which the electrode is inserted, that is, between the maternal abdominal wall and the acardiac twin, consists of the maternal skin (epithelial tissue and connective tissue), muscular layer (muscle tissue and connective tissue), the peritoneum (connective tissue), and the uterine wall (epithelial tissue, muscle tissue, and connective tissue). The layers are composed of epithelial tissue, muscle tissue, and connective tissue, and these tissues have similar characteristics to those involved in electrode insertion for ablation of malignant liver tumors. Furthermore, there are many blood vessels and sufficient blood flow around the umbilical cord insertion site of the acardiac twin (which is the coagulation/ablation target area), similarly to malignant liver tumors and surrounding normal liver tissue. In fact, the basic procedures of the RFA System for the proposed intended use (inserting the electrode cannula into the target site and performing coagulation and ablation) is similar to those for the initially approved intended use. The characteristics of the region around the coagulation/ablation site are unlikely to affect the performance of the RFA System even when anatomical differences are taken into account.

PMDA therefore concluded that, among the proposed performance and safety specifications, there is no particular problem in using the same performance specifications as those approved at the initial approval.

2.(2) Safety specifications

2.(2).1) Electrical safety and electromagnetic compatibility

2.(2).1).A Summary of the data submitted

The applicant submitted data relating to the electrical safety and electromagnetic compatibility of the RFA System: the certificates of analysis indicating the conformity of the electrode and generator to the proposed specifications for performance and safety (IEC60601-1:2007 and IEC60601-2-2:2009). The conformity to both specifications was confirmed by the certificates. The conformity of the generator to IEC60601-1-2:2010 (one of the proposed performance and safety specifications) was confirmed not by new testing (which was considered unnecessary based on the results of the risk analysis), but by the certificate of analysis indicating the conformity of the generator to IEC60601-1-2:2001.

2.(2).1).B Outline of the review conducted by PMDA

PMDA reviewed the electrical safety and electromagnetic compatibility data, and concluded that there was no particular problem.

2.(2).2) Physicochemical properties, biological safety, mechanical safety, and stability and durability

2.(2).2).A Summary of the data submitted

The applicant did not submit evaluation data relating to physicochemical properties, biological safety, mechanical safety, and stability and durability, because no changes were made to the specifications or components of the RFA System between the initial approval and the present partial change application.

2.(2).2).B Outline of the review conducted by PMDA

The submitted data do not include data relating to physicochemical properties, biological safety, mechanical safety, and stability and durability. PMDA considered this omission was acceptable because no changes were made to the specifications or components of the RFA System between the initial approval and the present partial change application.

2.(3) Performance

2.(3).A Summary of the data submitted

No changes were made to the specifications or components of the RFA System between the initial approval and the present partial change application. In the treatment of both acardiac twinning and malignant liver tumors, the electrode is inserted into similar tissues, namely tissue layers composed of epithelial tissue, muscle tissue, and connective tissue. Furthermore, the umbilical cord insertion site of the acardiac twin (the coagulation/ablation target area) is composed of soft tissue with many blood vessels and sufficient blood flow, similarly to malignant liver tumors and surrounding normal liver tissue.

There are thus no differences in (1) the degree of difficulty of insertion, (2) easiness in deployment of the distal tip of the electrode cannula, or (3) the coagulation or ablation characteristics regardless of treatment target. This means that performance of the RFA System in the treatment of acardiac twinning can be evaluated based on data from the performance tests conducted for the initial approval of the RFA System. Data relating to performance were therefore not submitted for the present partial change application.

2.(3).B Outline of the review conducted by PMDA

PMDA's conclusion:

Because no changes have been made to the specifications and components, the performance of the RFA System can be assured by the performance test results submitted for the initial approval, and thus data relating to performance need not be submitted for the present partial change application.

3. Conformity to the Requirements Specified in Paragraph 3 of Article 41 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics

3.A Summary of the data submitted

The applicant declared that the RFA System conforms to the requirements for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Ministry of Health, Labour and Welfare [MHLW] Ministerial Announcement No.122 of 2005; hereinafter referred to as "Essential Principles"), and Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Medical Devices and *In Vitro* Diagnostics (MHLW Ministerial Ordinance No. 169 of 2004).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of the RFA System to the Essential Principles.

The following passage describes PMDA's conclusion on the conformity of the RFA System to Article 1, which defines the preconditions for designing of medical devices (particularly, the requirements for users, such as expected level of technical knowledge and experience, and expected level of education and training to be provided to users):

As discussed in Section "6.B.(2) Efficacy and safety," in particular, "6.B.(2).2) Safety," and Section "6.B.(3) Post-marketing safety measures"], selection of qualified users and suitable facilities, and compliance with the guidelines on proper use are critical to maintaining the risk-benefit balance of the RFA System. PMDA has therefore decided to impose conditions of approval to ensure that necessary measures are taken.

Based on the above, PMDA comprehensively reviewed the conformity of the RFA System to the Essential Principles, and concluded that there was no particular problem.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted a summary of risk management measures carried out for the RFA System (its implementation system and its implementation status), in accordance with EN ISO 14971 "Medical devices—Application of risk management to medical devices."

4.B Outline of the review conducted by PMDA

PMDA reviewed documents on risk management and comprehensively concluded that there was no particular problem with the risk management, taking into consideration the issues discussed in Section "*3.B Outline of the review conducted by PMDA.*"

5. Manufacturing Process

5.A Summary of the data submitted

Data relating to the manufacturing process were not submitted because no changes were made to the manufacturing process of the RFA System between the initial approval and the present partial change application.

5.B Outline of the review conducted by PMDA

PMDA has concluded that data relating to the manufacturing process need not be submitted because no changes have been made to the manufacturing process of the RFA System.

6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare

6.A Summary of the data submitted

The applicant submitted a clinical evaluation report for the present partial change application. The report describes the evaluation of (a) the outcome of the pump twin under expectant management and (b) the efficacy and safety of RFA of the acardiac twin using the RFA System or other devices, based on published literature and Japanese and foreign guidelines.

Japanese and foreign textbooks and guidelines recommend radiofrequency ablation for the treatment of acardiac twinning. Acardiac twinning is a rare anomaly, and only 15 to 20 cases annually are estimated to be eligible for the treatment with the RFA System in Japan. However, based on reported cases alone, at least 170 cases of RFA have been performed to treat acardiac twinning in and outside Japan. These circumstances mean that any clinical study, even if conducted, is unlikely to provide information significant enough to affect the risk-benefit evaluation of the RFA System, and that the RFA System for the treatment of acardiac twinning can be evaluated based on published literature and other data.

6.A.(1) Published literature used in the clinical evaluation report and its selection procedure

A literature search was performed in the following databases from the year data listing began, shown in parentheses, up to January 2017: MEDLINE (from 1950), Embase (from 1974), and *Igaku Chuo Zasshi* (from 1983). The survey was conducted by OR search for each search topic (Table 5). Search terms were "TRAP sequence," "natural history," and "human" for Search Topic A; "TRAP sequence," "treatment techniques including RFA," and "human" for Search Topic B; and "TRAP sequence," "RFA," and "adverse events" for Search Topic C.

Table 5. Literature search topics

Search Topic A	The outcome of pump twins when acardiac twinning is untreated (e.g., survival rate).
Search Topic B	The outcome of pump twins after RFA of the acardiac twin (e.g., survival rate).
Search Topic C	Adverse events in the mother and pump twin after RFA of the acardiac twin.

The survey showed that 636 pieces of literature were applicable for Search Topics A, B, or C including duplicates (118 in MEDLINE; 185 in Embase; and 333 in *Igaku Chuo Zasshi*). These include systematic reviews, major textbooks and academic society guidelines published in and outside Japan, and the following original papers:

Search Topic A: Original papers reporting at least 5 cases of pump twin outcome under expectant management.

Search Topic B: Original papers reporting at least 5 cases of pump twin outcome after RFA of the acardiac twin.

Search Topic C: Original papers reporting adverse events in the mother and pump twin after RFA of the acardiac twin (regardless of the number of cases reported).

In total, 15, 20, and 20 pieces of literature, respectively, were identified for Search Topics A, B, and C. Of the 15 pieces for Search Topic A, 2 pieces (papers written in 1953 and 1960) were excluded because the diagnostic techniques described in the papers were completely different from the current ones; the remaining 13 pieces of literature were evaluated. The 20 pieces for Search Topic B are the same 20 pieces identified for Search Topic C. Of the 20 pieces, 8 were excluded because they were probably reported from the same facility; the remaining 12 pieces of literature were evaluated.

A total of 25 pieces of literature used for the clinical evaluation report are shown in Table 6 (Search Topic A), and Table 7 (Search Topics B and C).

Table 6. Literature concerning "the outcome of pump twins when acardiac twinning is untreated (e.g., survival rate)" (Search Topic A)

Literature No.	Title/author/source
1	Twin Reversed Arterial Perfusion Sequence (TRAPS): An Illustrative Series of 13 cases Ruiz-Cordero R, et al. *Fetal Pediatr Pathol.* 2016;35:63-80.
2	Treatment of twin reversed arterial perfusion sequence with alcohol ablation or bipolar cord coagulation Corbacioglu A, et al. *Int J Gynaecol Obstet.* 2012;117:257-9.
3	Prenatal diagnosis and outcome of multiple pregnancies with reversed arterial perfusion (TRAP-sequence) Hartge DR, et al. *Arch Gynecol Obstet.* 2012;286:81-8.
4	The outcome of twin reversed arterial perfusion sequence diagnosed in the first trimester Lewi L, et al. *Am J Obstet Gynecol*. 2010;203:213.e1-4.
5	Perinatal Outcome of Conservative Management versus Fetal Intervention for Twin Reversed Arterial Perfusion Sequence with a Small Acardiac Twin Jelin E, et al. *Fetal Diagn Ther.* 2010;27:138-41.
6	Surgical management of twin reversed arterial perfusion sequence Quintero RA, et al. *Am J Obstet Gynecol.* 2006;194:982-91.
7	The management of acardiac twins: a conservative approach Sullivan AE, et al. *Am J Obstet Gynecol.* 2003;189:1310-3.
8	Utility of Doppler velocimetry in predicting outcome in twin reversed-arterial perfusion sequence Dashe JS, et al. *Am J Obstet Gynecol.* 2001;185:135-9.
9	Prognostic Markers in Twin Pregnancies with an Acardiac Fetus Brassard M, et al. *Obstet Gynecol.* 1999;94:409-14.
10	Acardiac twins: pathophysiology, diagnosis, outcome and treatment. Six cases and review of the literature. Søgaard K, et al. *Fetal Diagn Ther.* 1999;14:53-9.
11	Acardia: predictive risk factors for the co-twin's survival Healey MG. *Teratology.* 1994;50:205-13.
12	Perinatal outcome of forty-nine pregnancies complicated by acardiac twinning. Moore TR, et al. *Am J Obstet Gynecol.* 1990;163:907-12.
13	Twin reversed arterial perfusion (TRAP) sequence: a study of 14 twin pregnancies with acardius. Van Allen MI, et al. *Semin Perinatol.* 1983;7:285-93.

Table 7. Literature concerning "the outcome of pump twins after RFA of the acardiac twin (e.g., survival rate)" and "adverse events in the mother and pump twin after RFA of the acardiac twin" (Search Topics B and C)

Literature No.	Title/author/source
14	Intervention versus a conservative approach in the management of TRAP sequence: a systematic review Mone F, et al. *J Perinat Med.* 2016;44:619-29.
15	Systematic review and metaanalysis of perinatal outcomes after radiofrequency ablation and bipolar cord occlusion in monochorionic pregnancies Gaetry K, et al. *Am J Obstet Gynecol.* 2015;213:637-43.
16	Optimal Method and Timing of Intrauterine Intervention in twin Reversed Arterial Perfusion Sequence: Case Study and Meta-Analysis Chaveeva P, et al. *Fetal Diagn Ther.* 2014;35:267-79.
17	Acardiac twin: a systematic review of minimally invasive treatment modalities Tan TYT, et al. *Ultrasound Obstet Gynecol.* 2003;22:409-19.
18	Clinical Outcomes after Selective Fetal Reduction of Complicated Monochorionic Twin with Radiofrequency Ablation and Bipolar Cord Coagulation Peng R, et al. *Gynecol Obstet Invest.* 2016;81:552-8.
19	Forty cases of twin reversed arterial perfusion sequence treated with radio frequency ablation using the multistep coagulation method: a single-center experience Sugibayashi R, et al. *Prenat Diagn.* 2016;36:437-43.
20	Radiofrequency Ablation with an Internally Cooled Electrode for Twin Reversed Arterial Perfusion Sequence Wagata M, et al. *Fetal Diagn Ther.* 2016;40:110-5.
21	Early vs late intervention in twin reversed arterial perfusion sequence Berg C, et al. *Ultrasound Obstet Gynecol.* 2014;43:60-4.
22	Perinatal- and procedure-related outcomes following radiofrequency ablation in monochorionic pregnancy Kumar S, et al. *Am J Obstet Gynecol.* 2014;210:454.e1-6.
23	The North American Fetal Therapy Network Registry data on outcomes of radiofrequency ablation for twin-reversed arterial perfusion sequence Lee H, et al. *Fetal Diagn Ther.* 2013;33:224-9.
24	The use of radiofrequency in the treatment of twin reversed arterial perfusion sequence: a case series and review of the literature Cabassa P, et al. *Eur J Obstet Gynecol Reprod Biol.* 2013;166:127-32.
25	Perinatal outcome after selective feticide in monochorionic twin pregnancies van den Bos EM, et al. *Ultrasound Obstet Gynecol.* 2013;41:653-8.

6.A.(2) Summary of major papers

Tables 8 and 9 summarize major papers.

Table 8. Summary of literature concerning "the outcome of pump twins when acardiac twinning is untreated (e.g., survival rate)" (Search Topic A)

Literature No.	Objective/methods	Result
1 (The authors' own cases)	Objective: To study clinical and pathological characteristics of the mother and fetus with TRAP sequence. Methods: A retrospective analysis of medical information, histopathologic and imaging exams of placentas and fetuses of TRAP sequence cases collected at an obstetric institution in the US between 1990 and 2013.	Of 13 cases collected, 12 were twin pregnancies and 1 was a triplet pregnancy. Six pump twins survived, and 7 died (i.e., 3 fetal deaths and 4 postnatal deaths). Among the surviving 6 pump twins, 4 weighed between 1685 and 3135 g, whereas the respective 6 acardiac twins weighed between 358 and 1079 g. Gestational age at delivery was 31-38 weeks for surviving pump twins, 15-19 weeks for stillbirths, and 26-33 weeks for pump twins who died shortly after birth.
2 (The authors' own cases)	Objective: To evaluate perinatal outcome of TRAP sequence pregnancies. Methods: The perinatal outcomes of 15 TRAP sequence pregnancies referred to an obstetric hospital in Turkey were evaluated.	Of the 15 cases, 6 were placed under expectant management. Alcohol ablation was performed in 5 cases, and bipolar umbilical cord coagulation was performed in 4 cases. Of the 15 cases, 12 showed a worsened condition of the pump twins during pregnancy, with an abdominal circumference ratio (acardiac/pump twin) of >50%. Of the 6 cases placed under expectant management, 3 had an abdominal circumference ratio (acardiac/pump twin) of <50%. Of the 6 cases placed under expectant management, 3 resulted in intrauterine death of the pump twin. Of the 5 cases treated by alcohol ablation, 3 had a successful delivery (live births) at 36-38 weeks, whereas intrauterine death occurred in 1 case, and abortion in 1 case. Of the 4 cases treated with bipolar umbilical cord coagulation, 2 had a successful delivery (live birth) at 39 weeks, 1 had premature rupture of membranes and abortion at 18 weeks, and 1 terminated pregnancy due to ventriculomegaly.
3 (The authors' own cases)	Objective: To examine the prenatal diagnosis of TRAP sequence and pregnancy outcome in monochorionic twin pregnancies. Methods: A retrospective analysis of cases referred to an obstetric hospital (a tertiary referral center) over a period of 16.5 years. Pump twins were followed up for at least 6 months after birth.	Of 412 cases of monochorionic twin pregnancies, 6 had TRAP sequence pregnancies (incidence, 1.46%). Mean gestational age at diagnosis was 20.4 (13.1-28.0) gestational weeks. Decompensated heart failure of the pump twin occurred in 2 cases (at 31 and 32 weeks) and premature rupture of membranes in 2 cases, all of which resulted in a caesarean delivery. All pump twins were born prematurely but survived without detectable mid- or long-term sequelae. There were no cases of missed prenatal diagnosis or false-positive diagnosis of TRAP sequence. Mean weight of the acardiac twins was 1400 g (830-2800 g). In 5 of 6 cases, the karyotype was normal.
4 (The authors' own cases)	Objective: To examine mortality of patients with TRAP sequence from the first trimester to intervention at 16-18 weeks. Methods: A retrospective review of the outcomes of monochorionic twin pregnancies diagnosed with TRAP sequence in the first trimester.	In the first trimester, 26 pregnant patients were diagnosed with TRAP sequence. Two opted for termination of pregnancy, while 24 opted for prophylactic intervention to stop blood flow at 16-18 weeks. Spontaneous death of the pump twin occurred in 8 of 24 cases (33%) between diagnosis and treatment. Of the 24 cases, 5 (21%) had spontaneous arrest of blood flow, whereas 11 (46%) continued to have blood perfusion to the acardiac twin until 16-18 weeks.

Literature No.	Objective/methods	Result
5 (The authors' own cases)	Objective: To examine the outcomes of TRAP sequence pregnancies with a weight ratio (acardiac twin/pump twin) of ≤50%. Methods: The medical records of 76 pregnancies suspected to have TRAP sequence between 1994 and 2009 were reviewed. Of 21 cases of TRAP sequence with a weight ratio (acardiac twin/pump twin) of ≤50%, 3 were excluded (lost to follow-up in 1 case, and symptomatic abnormalities in the pump twin in 2 cases), and the remaining 18 cases were analyzed.	Of the 18 cases analyzed, 7 (39%) underwent RFA, and 11 (61%) were placed under expectant management. The survival rate of pump twins was 100% (7 of 7 cases) in the RFA group, and 91% (10 of 11 cases) in the expectant management group. Among the 11 cases undergoing expectant management, 3 showed no perfusion of the acardiac twin at the time of visit, with a survival rate of 66% (2/3), and the remaining 8 showed perfusion of the acardiac twin at the time of visit, with a survival rate of 88% (7/8). Among the cases undergoing expectant management with no perfusion in the acardiac twin, 1 had intrauterine death of fetus. There were no statistically significant differences in gestational age at delivery, birth weight of the pump twin, or survival rate of the pump twin between the RFA and expectant management groups even when stratified by the presence/absence of perfusion in the acardiac twin.
6 (The authors' own cases)	Objective: To examine recommendable management of TRAP sequence. Methods: A retrospective analysis of medical records of all patients with TRAP sequence referred to between 1993 and 2004. Patients were eligible for umbilical cord occlusion if they had abdominal circumference of the acardiac twin greater than that of the pump twin, polyhydramnios, abnormal Doppler blood flow of the pump twin, hydrops fetalis, or monoamniotic twins. Various surgical techniques were used for umbilical cord occlusion.	Of the 74 TRAP sequence cases studied, 65 were surgical candidates and 51 underwent umbilical cord occlusion. The perinatal survival in surgical candidates who had undergone umbilical cord occlusion was 65% (33 of 51 cases), in contrast to 42.9% (6 of 14 cases) in surgical candidates who did not undergo umbilical cord occlusion ($P = 0.1$). However, perinatal outcomes in cases who underwent umbilical cord occlusion were significantly better (22 of 28 cases; 78.5%; $P = 0.02$) if there was no disruption of the dividing membrane. Umbilical cord occlusion within the amniotic sac of the acardiac twin was possible in 23.5% of the cases with no incidence of premature rupture of membranes, with 83% survival, and with a significantly later gestational age at delivery (36 weeks).
7 (The authors' own cases)	Objective: To examine the outcome of acardiac twinning pregnancies placed under expectant management. Methods: A retrospective analysis of medical records of all acardiac twin pregnancies managed expectantly between 1994 and 2001.	Of the 10 cases identified, 9 pump twins survived, and 1 case resulted in fetal death. The mean gestational age at diagnosis, and at delivery was 20.3 and 34.2 weeks, respectively. The mean weights of the pump and acardiac twins were 2279 and 1372 g, respectively. The weight ratio of the acardiac twin to pump twin was ≥50% in 5 of the 10 pregnancies. Of the 9 cases with surviving pump twin, 4 showed cessation of blood flow in the acardiac twin and had a delivery at ≥36 weeks. In the 1 case of fetal death, the diagnosis of acardiac twining was given at 21 weeks, polyhydramnios was noted from 23 weeks, and the fetal death occurred at 29 weeks.
8 (The authors' own cases)	Objective: To examine the relationship between Doppler ultrasonography findings and pregnancy outcome in TRAP sequence pregnancies. Methods: Six cases undergoing Doppler ultrasonography for the diagnosis of TRAP sequence between 1990 and 1997 were reviewed. Umbilical artery resistive index was calculated, and the association of the resistive index difference between the pump and acardiac twin in each pair with the pregnancy outcome was evaluated.	Five of 6 pump twins survived. Although 5 cases had abnormally elevated Doppler index values, the outcomes of the pump twin was unrelated to the umbilical artery flow velocity systolic/diastolic ratio or resistive index value of the acardiac twin. The 3 cases with a favorable outcome of the pump twin had a resistive index difference of >0.20 between pump and acardiac twins. The 3 cases with a poor outcome of the pump twin had small resistive index differences (<0.05) between pump and acardiac twins.

Literature No.	Objective/methods	Result
9 (The authors' own cases)	Objective: To identify ultrasonographic variables that can help predict the outcome of the pump twin in TRAP sequence pregnancies. Methods: Of 10 cases of TRAP sequence pregnancies, 9 could be followed up. Death, cardiac failure, and delivery at <30 weeks of gestational age were defined as adverse outcomes. The pulsatility index of the umbilical arteries of the pump and acardiac twins was measured.	Four of the 9 cases resulted in death of the pump twin: intrauterine fetal death (at 22 weeks) in 2 cases and serious cardiac failure (at 26 and 31 weeks) after caesarean delivery in the other 2 cases. The remaining 5 cases had a favorable outcome. The outcomes were not correlated with cardiothoracic ratio of the pump twin, the presence of cysts of the acardiac twin, or the presence of rudimentary heart. The pulsatility index of the acardiac twin was significantly lower than that of the pump twin. Poor outcomes were correlated with an elevated fractional shortening of the left ventricle in the second trimester, and with a rapid growth of the acardiac twin.
10 (The authors' own cases)	Objective: To examine the pathophysiology, diagnosis, outcome, and treatment of 6 acardiac twin pregnancies in a single institution. Methods: Six pregnancies diagnosed with an acardiac twin by ultrasonography between 1993 and 1997 were studied.	All 6 cases were managed expectantly. Five were twin pregnancies, and 1 was a triplet pregnancy. Of the 6 cases, 1 achieved the survival of the pump twin (successful delivery at 31 gestational weeks), 3 resulted in death of the pump twin soon after birth (delivery at 28, 29, and 30 gestational weeks), 1 resulted in intrauterine fetal death, and 1 resulted in termination of pregnancy.
11 (The author's own cases)	Objective: To examine factors predictive of the outcome of the pump twin in TRAP sequence pregnancies. Methods: A retrospective analysis of the cases reported in MEDLINE between 1960 and 1991, as well as 5 cases from the author's own institution. A total of 184 cases (166 twin pregnancies, 14 triplet pregnancies and 1 conjoined twin pregnancy) were reviewed in terms of the anatomy of the acardiac twins and ultrasonography findings before birth.	The mean gestation age at delivery was 31.1 weeks, which was more premature than that of normal twins (36.8 weeks). The mortality of the pump twin was 35% in twins, and 45% in triplets. Pump twin mortality were related to premature delivery before 32 weeks of gestation, an acardiac twin with a head, and an acardiac twin with arms, ears, larynx, trachea, pancreas, kidneys, or small intestine.
12 (The authors' own cases)	Objective: To examine factors associated with the outcome of acardiac twin pregnancies. Methods: A retrospective analysis of 49 cases was performed based on delivery records, neonatal records, and pathological findings at a university hospital in the US.	The mortality of the pump twin was 55%, primarily as a result of fetal prematurity. The mean gestational age at delivery was 29 ± 7.3 weeks, the mean birth weight of the pump twin was 1378 ± 1047 g, the mean weight of the acardiac twin was 651 ± 571 g. Polyhydramnios and premature delivery were related to the weight ratio of the acardiac twin to pump twin. The mean weight ratio of the acardiac twin to pump twin was 52% ± 42% in all cases, 60% in cases of premature delivery at <34 gestational weeks, and 29% in cases of delivery at ≥34 gestational weeks ($P < 0.04$). Premature delivery was strongly correlated with the development of polyhydramnios and cardiac failure of the pump twin ($P < 0.01$). The incidence of premature delivery, polyhydramnios, and cardiac failure, respectively, was 90%, 40%, and 30% in cases with an acardiac/pump twin weight ratio of ≥70%, and 75%, 30%, and 10% in cases of an acardiac/pump twin weight ratio of <70% ($P < 0.05$). The weight of the acardiac twin was expressed as $1.2\ L^2 - 1.7\ L$ (L = the longest length of the acardiac twin), and the correlation coefficient was 0.79 ($P < 0.01$).
13 (The authors' own cases)	Objective: To examine the morphology of the acardiac twin in TRAP sequence pregnancies, and abnormal vascular anastomosis in the placenta. Methods: A retrospective analysis of TRAP sequence pregnancies: 12 cases collected in an institution in the US, and 14 cases provided by 2 collaborating researchers.	Information on the placenta was obtained from 10 cases, all of which had arterio-arterial anastomosis and veno-venous anastomosis. Of the 10 cases, 6 were diamniotic twins, and 4 were monoamniotic twins. Of the 14 pump twins, 5 survived, 5 died, and 4 had an unknown outcome. Premature delivery occurred in 7 of the 14 cases. The 5 dead pump twins underwent autopsy; all of them had cardiomegaly, hepatomegaly, ascites, and growth restriction. No structural anomalies were found in pump twins.

Table 9. Summary of literature concerning "outcome of pump twins after RFA of the acardiac twin (e.g., survival rate)" and "adverse events in the mother and pump twin after RFA of the acardiac twin" (Search Topics B and C)

Literature No.	Number of cases	Survival rate	Adverse event
14 (Systematic review)	227	80.6% (183/227) (including other treatment methods)	Intrauterine fetal death: 19.4% (44/227)
15 (Systematic review)	156	79.1% (121/153)	Intrauterine fetal death: 14.7% (47/320) (including other diseases) Abortion: 5.3% (7/133) (including other diseases) Premature rupture of membranes at <37 weeks: 17.7% (39/220) (including other diseases) Premature delivery at <32 weeks: 23.7% (50/211) (including other diseases)
16 (Systematic review)	108	80.8%	—
17 (Systematic review)	13	84% (26/31) (including other treatment methods)	Intrauterine fetal death: 13% (4/31) (including other treatment methods) Premature rupture of membranes at <32 weeks: 23% (7/31) (including other diseases) Premature rupture of membranes within 2 weeks of the RFA procedure: 19% (6/31) (including other diseases)
18 (The authors' own cases)	12	64.3% (9/14) (including other treatment methods)	Premature rupture of membranes at <37 weeks: 33.3% (14/45) (including other diseases) Premature delivery at <28 weeks: 35.6% (16/45) (including other diseases) Premature delivery at <37 weeks: 71.1% (32/45) (including other diseases)
19 (The authors' own cases)	40	85% (34/40)	Intrauterine fetal death/abortion: 12.5% (5/40) Premature rupture of membranes at <34 weeks: 2.9% (1/35) Premature delivery at <34 weeks: 8.6% (3/35)
20 (The authors' own cases)	25	88% (22/25)	Intrauterine fetal death: 12% (3/25) Premature rupture of membranes at <32 weeks: 8% (2/25) Premature rupture of membranes at <37 weeks: 32% (8/25) Premature delivery at <32 weeks: 23% (5/22) Premature delivery at <37 weeks: 64% (14/22)
21 (The authors' own cases)	7	100% (7/7)	Death neonatal: 14.3% (1/7) Premature rupture of membranes at <37 weeks: 42.9% (3/7) Premature delivery at <37 weeks: 71.4% (5/7)
22 (The authors' own cases)	12	75% (9/12)	Intrauterine fetal death/abortion: 25% (3/12) Premature delivery at <34 weeks: 26.9% (21/78) (including other diseases)
23 (The authors' own cases)	98	83.7% (82/98)	Intrauterine fetal death: 16.3% (16/98) Death neonatal: 4.1% (4/98) Premature rupture of membranes at <37 weeks: 17.3% (17/98)
24 (The authors' own cases)	7	71.4% (5/7)	Intrauterine fetal death: 14.3% (1/7) Termination of pregnancy: 14.3% (1/7) Premature rupture of membranes at <37 weeks: 57.1% (4/7) Premature delivery: 57.1% (4/7)
25 (The authors' own cases)	5	80% (4/5)	Intrauterine fetal death: 36.4% (4/11) (including other diseases) Premature rupture of membranes at <37 weeks: 9.1% (1/11) (including other diseases)

6.A.(3) Evaluation of literature data on the efficacy of RFA of the acardiac twin

The outcome of a pump twin in acardiac twinning varies depending on the presence of blood flow from the pump twin to the acardiac twin, the size of the acardiac twin, and the degree of cardiac load in the pump twin. Expectant management is applicable in acardiac twin pregnancies with fewer exacerbating factors (e.g., the absence of blood flow from the pump twin to the acardiac twin, or a small acardiac twin compared with the pump twin). The pump twin survival rate was reported to be 42.9% (6 of 14 patients) in patients who were eligible for RFA but managed expectantly.[6]

According to systematic reviews summarizing the reports on RFA of the acardiac twin in foreign countries, the pump twin survival rate was around 80%,[14-17] suggesting that survival rate of the pump twin can be improved by RFA.

In Japan, the survival rate of the pump twin was >85% based on the outcome data of patients who underwent RFA of the acardiac twin.[19, 20]

6.A.(4) Evaluation of literature data on the safety of RFA of the acardiac twin

Adverse events in patients undergoing RFA of the acardiac twin are divided into those occurring in the mother and those occurring in the pump twin (both in the fetal and neonatal periods). Maternal adverse events associated with RFA include thermal burns at the site of the grounding pad, intrauterine infections, and chorioamnionitis (Table 10). There were no reports of serious adverse events in mothers who underwent RFA of the acardiac twin in Japan or foreign countries.

Adverse events reported in pump twins include premature rupture of membranes, premature delivery, abortion, intrauterine fetal death, and another RFA procedure due to resumption of blood flow after the first RFA (all occurring in the fetal period); and death neonatal (occurring in the neonatal period) (Tables 9 and 11). RFA of the acardiac twin is accompanied by certain risks of premature rupture of membranes and premature delivery. If this primary disease remains untreated, however, it may worsen and lead to deteriorated condition of the pump twin, and eventually to a premature delivery by caesarean section. The risks associated with RFA are therefore acceptable when weighed against the treatment benefits of RFA.

Table 10. Maternal adverse events after RFA of the acardiac twin

Adverse event (complication)	Literature	
	Outside Japan	In Japan
Maternal thermal burn (at the site of the grounding pad)	23	19
Intrauterine infection	18	–
Chorioamnionitis	21	–

Table 11. Adverse events occurring in pump twins after RFA of the acardiac twin

Literature		Number of patients treated with RFA	Number of patients with adverse events (incidence)	Adverse event (complication)
In Japan	19	40	1 (2.5%)	Premature rupture of membranes at <34 weeks
			3 (7.5%)	Premature delivery at <34 weeks
	20	25	2 (8.0%)	Premature rupture of membranes at <32 weeks
			5 (20.0%)	Premature delivery at <32 weeks
Outside Japan	15[*1]	220	39 (17.7%)	Premature rupture of membranes at <37 weeks
		211	50 (23.7%)	Premature delivery at <32 weeks
	17[*1]	31	7 (22.6%)	Premature rupture of membranes at <32 weeks
			6 (19.4%)	Premature rupture of membranes within 2 weeks of the procedure
	18[*1]	45	14 (31.1%)	Premature rupture of membranes at <37 weeks
			16 (35.6%)	Premature delivery at <28 weeks
			32 (71.1%)	Premature delivery at <37 weeks
	21	7	3 (42.9%)	Premature rupture of membranes at <37 weeks
			5 (71.4%)	Premature delivery at <37 weeks
	22[*1]	78	21 (26.9%)	Premature delivery at <34 weeks
	23	98	17 (17.3%)	Premature rupture of membranes at <37 weeks
			2 (2.0%)	Undergoing another RFA procedure due to resumption of blood flow after the first RFA
	24	7	4 (57.1%)[*2]	Premature rupture of membranes at <37 weeks
	25[*1]	11	1 (9.1%)	Premature rupture of membranes at <37 weeks

[*1], Including patients with conditions other than acardiac twinning who were treated with RFA.
[*2], One of the patients terminated pregnancy because she experienced premature rupture of membranes at 21 weeks and 4 days of gestation.

6.A.(5) Efficacy and safety

A retrospective analysis has reported on the efficacy of the RFA System used in patients in Japan who underwent RFA of the acardiac twin.[19] Table 12 shows the main pregnancy outcomes of 40 patients who underwent RFA between 2002 and 2015; all of them were eligible for RFA because they had an acardiac/pump twin abdominal circumference ratio of ≥1.0, polyhydramnios, perfusion anomaly, or hydrops fetalis. In Japan, pump twins treated with the RFA System have a survival rate of 85%, which is similar to those described in other reports (Table 9). The safety profile of the RFA System showed no adverse events specific to the device, and adverse events occurring in patients treated with the RFA System were similar to those described in other reports.

Table 12. Pregnancy outcomes of patients who underwent RFA of the acardiac twin using the RFA System in Japan

Pump twin survival rate	85% (34/40)
Pump twin intrauterine death	12.5% (5/40)
Infantile death of the pump twin	2.9% (1/40)
Premature rupture of membranes at <34 weeks	2.9% (1/40)
Premature delivery at <34 weeks	8.6% (3/40)
Gestational age at delivery of surviving pump twins	37.5 ± 3.5 weeks
Birth weight of surviving pump twins	2651 ± 600 g

6.A.(6) Clinical practice in Japan regarding treatment of acardiac twinning

The clinical practice in Japan regarding the treatment of acardiac twinning has been investigated and reported by a study conducted between January 2000 and October 2013.[26] This study was a retrospective analysis of medical records of 73 cases of acardiac twin pregnancies treated at Miyagi Children's Hospital, National Center for Child Health and Development, Showa University Hospital, Seirei Hamamatsu General Hospital, Nagara Medical Center, Osaka Women's and Children's Hospital, and Tokuyama Central Hospital (Table 13). In Japan, RFA is the most frequently used technique for the treatment of the acardiac twinning, and the outcome of the 73 cases did not differ significantly from that of other reports (Table 9).

Table 13. Outcome of treatment of acardiac twinning in Japan by treatment technique

Treatment technique	Number of patients treated	Survival rate at 30 days after birth[*1]
RFA	77% (56/73)	88% (28/32)
Fetoscopic laser photocoagulation	16% (12/73)	83% (10/12)
High-intensity focused ultrasound	5% (4/73)	50% (2/4)
Bipolar umbilical cord coagulation	1% (1/73)	Unknown

[*1], Only analyzable patient data were evaluated.

6.A.(7) Awareness of RFA of the acardiac twin in and outside Japan

Radiofrequency ablation is widely recognized as a treatment option of acardiac twinning and has actually been performed in and outside Japan. RFA is recommended or listed as a safe and effective treatment option for acardiac twinning in Japanese and foreign guidelines and textbooks and in manuals issued by maternal and fetal medicine specialist groups in Japan (Table 14).

Table 14. Summary of descriptions on RFA of the acardiac twin in guidelines and other publications published in and outside Japan

Title	Summary
Guidelines for Obstetrical Practice in Japan (2017)[27]	Pump twins may experience cardiac failure because it is responsible for blood supply to the TRAP sequence via anastomotic vessels (arterio-arterial anastomosis). If the acardiac/pump twin weight ratio is ≥50%, the mortality of the pump twin is 45%. The larger the acardiac twin, the higher the mortality of the pump twin. Further, a study reported that among patients diagnosed with TRAP sequence pregnancies in the first trimester, fetal death of the pump twin occurred in 33% of patients by 16-18 weeks, while natural arrest of blood supply to the TRAP sequence occurred in 21% of patients. Treatment options for terminating blood flow to the TRAP sequence (e.g., radiofrequency, bipolar diathermy, and laser) are available to reduce the excessive cardiac load on the pump twin (i.e., to prevent cardiac failure in the pump twin). The survival rate of the pump twin was reported to be 43% in patients who were eligible for treatment but remained untreated. Radiofrequency thermal ablation of the acardiac twin is minimally invasive and used most frequently, with a pump twin survival rate of ≥80%. RFA is effective in the treatment of TRAP sequence at ≥15 weeks of gestation.
SMFM Clinical Guideline (2015)[28]	Radiofrequency ablation is recommended for the treatment of TRAP sequence, especially for acardiac twinning with severe complications including hydrops fetalis.
Williams Obstetrics. 24th edition (2014)[29]	• A survival rate of approximately 90% was achieved by RFA in the second trimester of pregnancy. • TRAP sequence-associated mortality is high during the first trimester of pregnancy, and there are very few reports on early intervention. Procedures that can be safely performed before fusion of the chorion and the amnion are not presented.
Fetology. 2nd edition (2010)[30]	The survival rate of pump twins was 91% in patients who underwent RFA.[23]
Manual of Maternal and Fetal Intensive Care Unit (MFICU). 3rd revised edition, edited by Liaison Association of National Perinatal Care (2015)[31]	• Cardiac failure or polyhydramnios may occur in the pump twin, and RFA is regarded as an effective treatment for patients with these conditions. • Intrafetal ablation has reportedly been performed by alcohol, monopolar diathermy, laser, and radiofrequency energy. The survival rate of the fetus after RFA is reported to be 71%-92%. • Radiofrequency ablation is the most frequently used technique for the treatment of acardiac twinning in Japan.
Website of Japan Fetal Therapy Group[32] (http://fetusjapan.jp/)	Radiofrequency ablation is the main treatment option for TRAP sequence in Japan.

6.B Outline of the review conducted by PMDA

PMDA conducted a review focusing primarily on the following issues.

6.B.(1) Appropriateness of literature-based clinical evaluation

PMDA's view on the appropriateness of conducting clinical evaluation of the RFA System based on literature:

Since 2000, RFA of the acardiac twin has been performed in many patients with acardiac twinning. Radiofrequency ablation is recommended in the Guidelines for Obstetrical Practice in Japan (2017)[27] and SMFM Clinical Guideline (2015),[28] and is listed in textbooks published in and outside Japan as one of the treatment options. Acardiac twinning is a rare anomaly, and only 15 to 20 cases annually are estimated to be eligible for treatment with the RFA System in Japan. In and outside Japan, however, at least 170 cases of acardiac twinning have been treated with RFA, based on reported cases alone. These circumstances mean that radiofrequency ablation is already recognized as a viable treatment option by healthcare professionals, and that any clinical study, even if conducted, is unlikely to provide new information significant enough to affect the efficacy or safety profile of the RFA System.

In cases where the pump twin is likely to die unless blood flow from the pump twin to the acardiac twin is terminated, there are no effective therapies other than fetal treatment. The RFA System is therefore positioned as a life-saving device with significant clinical benefits. In addition, treatment options and procedures for acardiac twinning do not differ between Japan and foreign countries, and acardiac twinning is not affected by racial differences.

Based on comments from the Expert Discussion, PMDA concluded that even if bias is present in data from the literature reports, the risks and benefits of the RFA System can still be evaluated, and thus the efficacy and safety of RFA in the treatment of acardiac twinning should be evaluated based on the existing literature.

6.B.(2) Efficacy and safety

6.B.(2).1) Efficacy

PMDA's view on the efficacy of the RFA System in Japan:

Pump twins experiencing cardiac failure are known to have poor outcomes, and the survival rate of pump twins under expectant management has been reported to be 42.9%.[6] On the other hand, systematic reviews of foreign papers reported that RFA was capable of producing coagulation in a reliable and minimally invasive manner, with a pump twin survival rate of 80.8%.[16]

The efficacy of RFA of the acardiac twin does not differ significantly between Japan and foreign countries, because (a) both in and outside Japan, acardiac twinning is diagnosed by ultrasound, (b) a certain consensus exists among specialists about factors contributing to poor outcome, (c) treatment outcome immediately after the RFA procedure is determined by ultrasound, and (d) the survival rate of the pump twin is evaluated in a similar manner in and outside Japan. A clinical research and a survey of RFA were conducted in Japan. The research and survey are limited because of their retrospective nature but covered almost all of the institutions providing the treatment of acardiac twinning in Japan. Both the research and survey reported a pump twin survival rate of as high as 88% after RFA of the acardiac

twin.[20, 26] The RFA System showed a 85% survival rate of the pump twin although it was used in only 40 cases.[19]

PMDA has concluded that the RFA System has efficacy in patients in Japan, after reviewing the clinical evaluation report included in the present application and comprehensively evaluating the differences in healthcare environments between Japan and other countries.

6.B.(2).2) Safety

PMDA's view on the safety of the RFA System in Japan:

The following are the main adverse events reported from patients with acardiac twinning treated with the RFA System: "thermal burn at the site of the grounding pad," and "infections" in the mother; and "premature rupture of membranes" and "premature delivery" in the pump twin (Tables 10 and 11).

Maternal adverse events:

The RFA System is an electrical ablation instrument, and thermal burns at the site of the grounding pad were reported also in patients receiving treatment with the RFA System for the other indication (Tables 3 and 4). This suggests that this adverse event is not unique to the treatment of the acardiac twinning. As with the other indication, thermal burns can be prevented by paying attention to the location and number of grounding pads and to their unintentional removal from the skin. As for maternal infections, the RFA procedure requires insertion of an electrode cannula into the uterus, which poses the risk of infections in the mother; however, this risk can be reduced considerably by disinfection and administration of antibiotics.

Adverse events in pump twins:

Because the RFA procedure requires insertion of an electrode cannula into the uterus, premature rupture of membranes and premature delivery may inevitably occur at a higher incidence than in normal pregnancies without any treatment. The outcome of a pump twin, however, is reported to be extremely poor if it is managed expectantly despite being eligible for RFA treatment.[6] Treatment benefits therefore outweigh the risks of premature rupture of membranes and premature delivery at least in patients who have not reached the gestational weeks during which premature delivery significantly affects the survival of the pump twin. In contrast, expectant management is considered possible in patients with fewer factors contributing to worsening of the condition; therefore, determining patients' eligibility for treatment is critical, and it is also important to identify the optimal time to perform the procedure in cases where premature delivery significantly affects the survival of the pump twin.

To reduce the risks associated with RFA using the RFA System, RFA should be performed by physicians with (1) thorough knowledge of the pathology of acardiac twinning, (2) experience in fetal treatment, and (3) knowledge on how to avoid adverse events, at medical institutions equipped to provide emergency treatment for mothers and children on a routine basis, after identifying the necessity of the

treatment and suitable timing. PMDA concluded that, if these conditions are satisfied, the safety of the RFA System in Japan is clinically acceptable.

6.B.(3) Post-marketing safety measures

PMDA asked the applicant to explain the post-marketing safety measures to be implemented for the RFA System.

The applicant's response:

In Japan, RFA of the acardiac twin is performed off-label in routine clinical practice. Because acardiac twinning is a rare condition, only a limited number of medical institutions can provide this treatment. As of 2018, RFA of the acardiac twin is performed at only 6 institutions (National Center for Child Health and Development, Seirei Hamamatsu General Hospital, Osaka Women's and Children's Hospital, Nagara Medical Center, Miyagi Children's Hospital, and Fukuoka Children's Hospital). Consequently, in routine clinical practice, RFA has been performed by physicians with thorough knowledge of the pathology of acardiac twinning and experience in fetal treatment at medical institutions equipped to provide emergency treatment for mothers and children [read the risk reduction conditions described in Section "6.B.(2).2) Safety"], and these conditions must be complied with also after approval of the RFA System. Given the rarity of acardiac twinning and the specialized techniques required for RFA of the acardiac twin, the "guidelines on proper use" to be formulated by the relevant academic societies will include criteria for selecting eligible patients, requirements for physicians performing the procedure, requirements for medical institutions providing the procedure, use method, and the process of obtaining informed consent. The safety of the RFA System can therefore be assured by disseminating the guidelines on proper use and ensuring physicians' compliance with the guidelines; the package insert will therefore include a statement that instructs users to comply with the guidelines. The literature survey conducted so far has not revealed sufficient information on the long-term outcomes of pump twins born to women who had undergone RFA. Such information will therefore be gathered and investigated by the relevant academic societies. When the information becomes available, further risk reduction activities will be implemented as necessary.

Based on the guidelines on proper use to be formulated by the relevant academic societies, PMDA has concluded that the applicant's explanation was acceptable, and that the RFA System should be used in compliance with the guidelines on proper use and therefore conditions of approval should be imposed.

7. Plan for Post-marketing Surveillance etc. Stipulated in Paragraph 1 of Article 2 of Ministerial Ordinance on Good Post-marketing Study Practice for Medical Devices

7.A Summary of the data submitted

The applicant's explanation:

The clinical evaluation report provides clinical experience data in Japan, which are a summary of experience with RFA in routine clinical practice in Japan. This means that there is nothing left to be

revealed about the efficacy and safety of RFA by a new use-results survey and therefore a post-marketing use-results evaluation is unnecessary.

7.B Outline of the review conducted by PMDA

PMDA's view:

A post-marketing use-results survey is unlikely to identify new safety concerns, for the following reasons: (1) the submitted clinical experience data in Japan is a summary of experience with RFA in routine clinical practice; (2) acardiac twinning is a rare anomaly; and (3) only a limited number of cases can be collected in the post-marketing setting.

Only limited information is available on the long-term outcomes of pump twins born to women who had undergone RFA. Therefore the relevant academic societies (which submitted the petition for early introduction of RFA for acardiac twinning) will collect data on the long-term outcomes of pump twins. Perinatal safety information collected by the academic societies will be provided to healthcare professionals as necessary. The applicant plans to implement risk reduction activities as necessary based on the long-term outcomes to be revealed by the survey conducted by the academic societies.

The applicant, in cooperation with the relevant academic societies, will gather information on the long-term outcomes of pump twins born to women who had undergone RFA, and implement risk reduction measures for the RFA System based on information to be gathered. PMDA has concluded that these actions ensure the post-marketing safety of the RFA System, and that the RFA System should not be designated as a medical device subject to use-results evaluation.

III. Results of Compliance Assessment Concerning the New Medical Device Application Data and Conclusion Reached by PMDA

The new medical device application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

IV. Overall evaluation

The RFA System is a radiofrequency ablation system for coagulation of a malignant liver tumor or an acardiac twin. The present partial change application is intended to expand the indication to include the treatment of acardiac twinning. The main points discussed during the review of the RFA System are (1) the efficacy and safety; (2) post-marketing safety measures; and (3) use-results evaluation. Taking into account the comments from the Expert Discussion, PMDA has reached the conclusions described below.

(1) Efficacy and safety

Since 2000, many patients have undergone RFA for the treatment of acardiac twinning. RFA is a treatment option widely recognized by healthcare professionals, as recommended in guidelines published in and outside Japan. As for the efficacy of the RFA System, the clinical evaluation report demonstrated that treatment of acardiac twinning with RFA increased the survival rate of pump twins. In the evaluation of safety, the following adverse events were the main ones reported: thermal burns at the site of the grounding pad and infections in mothers; and premature rupture of membranes and premature delivery in pump twins. The risks for infections and thermal burns at the site of the grounding pad can be reduced by following the guidelines on proper use and ensuring appropriate post-operative management. In contrast, premature rupture of membranes and premature delivery inevitably occur at a higher incidence than in normal pregnancies without any treatment, because RFA requires intrauterine insertion of the electrode cannula. However, treatment benefits outweigh the risks of premature rupture of membranes and premature delivery, because the outcome of pump twins is reported to be extremely poor if they are managed expectantly despite being eligible for RFA treatment.

(2) Post-marketing safety measures

Because acardiac twinning is a rare condition, only a limited number of medical institutions provide treatment with RFA. While being used off-label, RFA has been performed by physicians with sufficient knowledge and experience at medical institutions equipped to provide emergency treatment for mothers and children. Therefore, after marketing approval, RFA of the acardiac twin should be performed at medical institutions equipped to provide emergency treatment either by a physician with sufficient experience in RFA of the acardiac twin, or by a physician with thorough knowledge of the pathology of acardiac twinning and sufficient experience in fetal treatment under supervision of a physician with sufficient experience in RFA of the acardiac twin. To minimize risks associated with the RFA System, physicians should determine the eligibility of patients, decide the optimal time to perform the procedure, and obtain informed consent in a proper manner. Further, physicians must be fully informed of the guidelines on proper use (which will be formulated in cooperation with the relevant academic societies), and must adhere to the guidelines when using the RFA System. To ensure these requirement are met, conditions of approval must be imposed.

(3) Use-results evaluation

A post-marketing use-results survey is unlikely to identify new safety concerns, for the following reasons: (1) the submitted clinical experience data in Japan is a summary of experience with RFA in routine clinical practice; (2) acardiac twinning is a rare anomaly; and (3) only a limited number of cases can be collected in the post-marketing setting.

The applicant, in cooperation with the relevant academic societies, will gather information on the long-term outcomes of pump twins born to women who had undergone RFA, and implement risk reduction measures for the RFA System based on information to be gathered. PMDA has concluded that these

actions ensure the post-marketing safety of the RFA System, and that the RFA System should not be designated as a medical device subject to use-results evaluation.

As a result of the above review, PMDA concludes that the RFA System may be approved after modifying the proposed wording for the intended use (the underlined words were added to the proposed text).

Intended Use

Radiofrequency coagulation and ablation of the following tissues:

1. Malignant liver tumor
2. Acardiac twinning (only for the purpose of blocking the blood flow to the acardiac twin)

Conditions of Approval

The applicant is required to take necessary actions, including providing training sessions and disseminating guidelines on proper use prepared in cooperation with relevant academic societies, to ensure that the product will be used by physicians with thorough knowledge and experience in radiofrequency ablation of acardiac twinning who have acquired skills required for using the RFA System and adequate knowledge of procedural complications, in compliance with the intended use and directions for use, at medical facilities capable of providing adequate medical care.

This application should be subject to deliberation by the Committee on Medical Devices and *In-vitro* Diagnostics.

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